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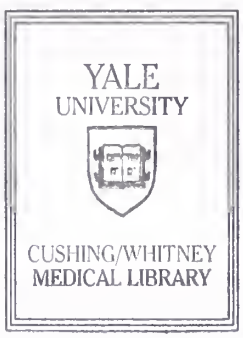
MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION IN VETERANS: A STUDY ACCORDING TO HOSPITAL SOPHISTICATION

Jody Alpert Levine

YALE UNIVERSITY

2000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MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION IN VETERANS: A STUDY ACCORDING TO HOSPITAL SOPHISTICATION

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

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ABSTRACT

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION IN VETERANS: A STUDY ACCORDING TO HOSPITAL SOPHISTICATION. Jody A. Levine and Michael D. Ezekowitz. Section of Cardiology, Department of Internal Medicine, Yale University, School of Medicine, New Haven, CT.

Employing baseline data from the CHAMP study, a prospective, randomized study of 5018 patients post acute myocardial infarction (AMI), conducted in the VA to evaluate aspirin/warfarin in combination versus aspirin, we investigated whether a relationship existed between the availability of resources and the type of medical care delivered. In addition, we assessed for temporal trends in pharmacologic treatment to determine if practice patterns reflect the results of clinical trials. Accordingly, participating hospitals were divided into three groups: group 1 did not perform cardiac catheterization procedures, angioplasty (PTCA), or cardiovascular surgery (CABG); group 2 performed cardiac catheterization procedures, but not PTCA or CABG; group 3 provided PTCA and CABG. Procedure and pharmacologic use were examined for each hospital group and plotted over time (1993-1997).

Patients admitted to group 3 hospitals were more likely to undergo "early" (within 14 days of AMI) PTCA (23.4%) as compared with other interventions, i.e., "later" (14-90 days after AMI) PTCA (8.8%), "early" CABG (7.69%), and "later" CABG (14.64%). The rate of "early" PTCA increased with increasing hospital sophistication: 5.04%, 8.55%, and 23.45% in groups 1, 2, and 3, respectively ($p=0.001$). For group 1, "later" CABG was more common compared with groups 2 and 3: 19.16% vs. 13.00% vs. 14.64%, respectively ($p=0.001$). In all hospital groups utilization rates of beta-blockers, ACE inhibitors, and hypolipidemic agents increased, while use of calcium channel blockers decreased ($p=0.001$ for each drug).

We conclude that procedure use in VA patients with AMI increased over time (1993-1997) and differed by level of hospital sophistication: greater "early" PTCA rate in sophisticated and greater "later" CABG rate in patients admitted to unsophisticated hospitals. The impact of these findings will be better understood when outcome analyses are performed. Trends in pharmacologic treatment provide evidence that clinical trial results are being translated into patient care.

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To my dear husband Elie and cherished daughters Skyler Brooke and Jasmine Paige, I extend much love and great appreciation. I thank you Elie for your unfailing support, encouragement, and love. You are a sensational father and husband, as well as my dearest friend. You have the perfect constitution to be an outstanding physician. Skyler and Jasmine, you fill my life with warmth, joy and excitement. You make every day wonderful!

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TABLE OF CONTENTS

I. Introduction 1

A. Preamble 1

B. Acute Myocardial Infarction 2

1. Definition 2

2. Incidence 3

3. Etiology, Classification and Outcome 4

4. Developments in Treatment 5

C. ACC/AHA Clinical Practice Guidelines: History and Format 6

D. Treatment Options 6

1. Thrombolysis 6

a. Rationale for Thrombolytic Therapy 6

b. General Mechanisms of Action 7

c. Adverse Effects 8

d. Overview of Clinical Trials 8

e. Recommendations 9

f. Contraindications and Cautions 10

g. Summary 10

2. Primary Percutaneous Transluminal Coronary Angioplasty (PTCA) 11

a. General Considerations 11

b. Overview of Clinical Trials 12

c. Limitations 13

d. Recommendations 14

e. Summary 14

3. Coronary Artery Bypass Graft Surgery (CABG) 14

a. General Considerations 14

b. Recommendations for Emergency or Urgent CABG 16
c. Summary 17
E. Rationale and Approach to Pharmacotherapy 17
1. Nitroglycerin 17
a. General Considerations and Mechanism of Action 17
b. Limitations and Adverse Effects 18
c. Overview of Clinical Trials 19
d. Summary 20
2. Aspirin and Other Platelet-Active Drugs 21
a. Mechanism of Action 21
b. Prevention of Thrombotic Complications of Atherosclerosis 21
c. Side Effects 22
d. Ticlopidine 23
3. Antithrombotics/Anticoagulants 23
a. Coagulation System 23
b. Heparin 24
1. Mechanism of Action 24
2. Overview of Clinical Trials 25
3. Recommendations 26
4. Antiarrhythmic Drugs 26
a. Introduction to Arrhythmia 26
b. General Mechanism of Antiarrhythmic Therapy 27
c. Adverse Effects 27
d. Specific Agents and Recommendations 28
1. Lidocaine 28
2. Bretylium 28
3. Procainamide 28

4. Beta-Adrenoceptor Blockers 29
5. Amiodarone 30
e. Summary 30
5. Beta-Adrenoceptor Blocking Agents 31
a. General Considerations 31
b. Coronary Effects 31
c. Adverse Effects 32
d. Overview of Clinical Trials 32
e. Recommendations for Early Therapy 33
f. Contraindications 34
g. Summary 34
6. Angiotensin Converting Enzyme Inhibitors 34
a. General Considerations 34
b. Coronary Effects 35
c. Adverse Effects 35
d. Overview of Clinical Trials 35
e. Recommendations 36
f. Summary 36
7. Calcium Channel Blockers 37
a. General Considerations 37
b. Coronary Effects 38
c. Adverse Effects 38
d. Specific Agents and Overview of Clinical Trials 38
1. Nifedipine 38
2. Verapamil 39
3. Diltiazem 39
e. Recommendations 39

f. Summary 40

8. Inotropic Agents 40

a. General Considerations 40

b. Digitalis 41

1. General Considerations 41

2. Mode of Action 42

3. Adverse Effects 42

4. Overview of Clinical Trials 43

9. Diuretics 44

10. Hypolipidemic Agents 44

II. Statement of Purpose and Hypothesis 45

III. Methods 46

A. Experimental Design 46

B. Data Source: The CHAMP Study 46

C. Data Acquisition Specifically Related to This Project 48

D. Statistical Methods 48

IV. Results 50

A. CHAMP Enrollment by Hospital Cardiac Capability 50

B. CHAMP Enrollment 1993-1998 50

C. CHAMP Trends in Procedure Use 50

1. CHAMP CABG Rates 50

a. Total CABG (Within 90 Days) Post-MI by Year 50

b. CABG Rates by Hospital Type 51

1. Early (Within 14 Days) vs. Later (Between 14 –90 Days) CABG Post-MI by Hospital Type 51

2. Total CABG (Within 90 Days) Post-MI by Hospital Type 51

c. CABG Rates by Hospital Type by Year 51
1. Early CABG (Within 14 Days) Post-MI by Hospital Type by Year 51
2. Later CABG (Between 14 - 90 Days) Post-MI By Hospital Type by Year 52
3. Total CABG (Within 90 Days)Post-MI by Hospital Type by Year 52
2. CHAMP PTCA Rates 53
a. Total PTCA (Within 90 Days) Post-MI by Year 53
b. PTCA Rates by Hospital Type 53
1. Early (Within 14 Days) Vs. Later (Between 14 – 90 Days) PTCA Post-MI by Hospital Type 53
2. Total PTCA (Within 90 Days) Post-MI by Hospital Type 53
c. PTCA Rates by Hospital Type by Year 53
1. Early PTCA (Within 14 Days) Post-MI by Hospital Type by Year 53
2. Later PTCA (Between 14-90 Days) Post-MI by Hospital Type by Year 54
3. Total PTCA (Within 90 Days) Post-MI by Hospital Type by Year 54
D. CHAMP Trends in Medication Use 54
1. Thrombolytics 54
a. Thrombolytic Use by Year 54
b. Thrombolytic Use by Hospital Type 55
c. Thrombolytic Use by Hospital Type by Year 55
2. ACE Inhibitors 55

a. ACE Inhibitor Use by Year 55
b. ACE Inhibitor Use by Hospital Type 55
c. ACE Inhibitor Use by Hospital Type by Year 55
3. Beta-Blockers 56
a. Beta-Blocker Use by Year 56
b. Beta-Blocker Use by Hospital Type 56
c. Beta-Blocker Use by Hospital Type by Year 56
4. Calcium Channel Blockers 56
a. Calcium Channel Blocker Use by Year 56
b. Calcium Channel Blocker Use by Hospital Type 56
c. Calcium Channel Blocker Use by Hosptial Type by Year 57
5. Digitalis 57
a. Digitalis Use by Year 57
b. Digitalis Use by Hospital Type 57
c. Digitalis Use by Hospital Type by Year 57
6. Diuretics 58
a. Diuretic Use by Year 58
b. Diuretic Use by Hospital Type 58
c. Diuretic Use by Hospital Type by Year 58
7. Nitrates 58
a. Nitrate Use by Year 58
b. Nitrate Use by Hospital Type 59
c. Nitrate Use by Hospital Type by Year 59
8. Hypolipidemic Agents 59
a. Hypolipidemic Agent Use by Year 59
b. Hypolipidemic Agent Use by Hospital Type 59
c. Hypolipidemic Agent Use by Hospital Type by Year 59

V. Discussion 61

VI. References 68

VII. Figure References and Legends 75

VIII. Tables 111

I. Introduction

A. Preamble

In this age of rapidly changing technology and advances in pharmacological therapy, increasing emphasis is being placed on analyzing our medical care system, its appropriateness and effectiveness. The Veterans Administration (VA) system , our largest national health system, is a particularly useful marker of our medical care system at large, isolating the medical care system from the variables of patients or doctors involved. The VA system serves a patient population that is sociodemographically homogeneous, has a highly centralized administrative structure, and contains physicians that are salaried and thus unable to maximize their revenue by altering their practice patterns. These factors make the VA system an excellent model for the evaluation of medical care practices. Increased analysis of the VA health care system, over the last several years, has resulted, as well, from a heightened commitment by the Department of VA health care toward revamping its structure in order to assure greater quality and efficiency of care.

In this study we employ data from the VA health care system to assess management patterns in patients diagnosed with acute myocardial infarction. We investigate the question of how patient care is dependent on the resources that are available--how hospital sophistication impacts medical practice patterns. In order to provide background to the treatment options available in the management of AMI, we first provide an extensive review of the literature. Standards of care are presented as ACC/AHA guidelines.

Another focus of this thesis is to determine whether the medical management employed by the VA health care system adheres to these clinical practice guidelines. Large, well-designed clinical trials have been conducted over several decades in patients with ischemic heart disease. Many have provided definitive results which have been translated into published guidelines, designated to provide standards for optimum patient

care. A number of organizations have developed such guidelines, including the American College of Cardiology (ACC) and the American Heart Association (AHA), in a joint effort. Clinical guidelines are of growing importance as technology rapidly progresses and there is a need to curb the cost of medical care; for, if adopted, they should impact the cost of medical care without diminishing its effectiveness. Guidelines are also meaningful for legal reasons as well as for payment of physicians from third party carriers.

Despite the effort that has been dedicated toward clinical trials and subsequent guidelines, translation of these studies and applications of guidelines in clinical practice is imperfect. There is evidence of a gap between how we actually manage and how we should be managing patients with ischemic heart disease. This study will, in part, investigate this concern. By accruing data over a six year time period, we study changes in practice patterns over time. We assess whether temporal trends in management of acute myocardial infarction (AMI) reflect the clinical trial results that were published during the time period under investigation. Since the results of clinical trials are ultimately translated into guidelines, our analysis will help to evaluate if the aforementioned gap exists in the VA system.

B. Acute Myocardial Infarction

1. Definition

A spectrum of clinical conditions ranging from unstable angina to non-Q wave AMI and Q wave AMI is referred to as "the acute coronary syndrome." Patients that present with ischemic chest pain at rest can be divided into those that show ST-segment elevation on initial 12-lead EKG and those that have no ST- segment elevation. There is a high probability that patients with ST-segment elevation have a thrombus occluding the "infarct-related" coronary artery and the majority of these patients develop a Q wave AMI. Nonetheless, not every ST elevation MI becomes a Q wave AMI and a minority of these patients do develop a non-Q wave AMI. Depending on the existence of serum cardiac markers such as CK-MB, patients that present initially without ST elevation usually are

diagnosed as either having a non-Q wave AMI or having unstable angina. A minority of these patients ultimately develop a Q wave AMI. Clinical distinction among these entities is retrospectively achieved following serial EKGs and serum cardiac markers. Acute myocardial infarction is generally considered the prime example of the acute coronary syndrome and is the entity on which we will focus from here on [1].

2. Incidence

Coronary artery disease is the single largest killer of males and females in the United States [2]. Approximately 1.5 million myocardial infarctions occur each year in the United States with a mortality rate of approximately 30%. Greater than half of these deaths occur before the individuals reach the hospital [3]. The American Heart Association statistics show that about every 29 seconds an American will suffer a coronary event, and about every minute someone will die from one. There are 13,900,000 people alive today--7,100,000 males and 6,800,000 females--with a history of heart attack, angina pectoris or both [2].

Despite a 47% reduction in age-adjusted coronary mortality rates over the previous 20 years, 514,000 people died of coronary disease in 1987 [4]. In 1995, coronary disease caused 481,287 deaths in the US--1 of every 4.8 deaths--and yet a decline in death rate of 28.7% from 1985. Among the patients who died from coronary disease in 1995, 244,819 (50.9%) were male and 236,468(49.1%) female. Death rates in 1995 from coronary disease were 124.4 for white males and 133.1 for black males (7.0% higher), 60.3 for white females and 81.6 for black females (35.3 % higher) [2].

Although the mortality rate following admission for myocardial infarction has encouragingly declined by about 30 % over the last two decades, approximately 1 of every 25 patients who survives initial hospitalization will die in the first year following myocardial infarction [3]. People who survive the acute stage of a heart attack have a chance of illness and death that is 2-9 times higher than that of the general population. The risk of another heart attack, sudden death, angina pectoris, heart failure and stroke, for both

men and women, is substantial [2] . For elderly patients (over age 65), survival is markedly decreased with a mortality rate of 20 percent at 1 month and 35 percent at 1 year following infarction [3] .

3. Etiology, Classification, and Outcome

Myocardial infarction is caused by prolonged myocardial ischemia, usually precipitated by an occlusive coronary thrombus at the position of a preexisting, though not always flow limiting, atherosclerotic plaque. Other, less frequent causes include prolonged vasospasm, insufficient myocardial blood flow (i.e., hypotension), or excessive metabolic demand. Rarer etiologies include occlusion by an embolus, vasculitis, aortic root or coronary artery dissection, or aortitis. In young individuals with no cardiac risk factors, cocaine may be the culprit.

The site and magnitude of infarction depend upon the distribution of the occluded vessel, the existence of additional stenotic lesions, and the sufficiency of collateral circulation. Classic electrocardiographic findings of the evolution of ST segment elevation to Q-waves marks the infarction as transmural. If pain, enzyme elevations, and ST-T wave changes occurred without Q-waves, however, the infarction is termed nontransmural or subendocardial. On pathologic examination infarctions primarily involve the subendocardium, with some transmural extension, even in the absence of Q-waves. Thus, the classification of infarctions as Q-wave versus non-Q-wave is more appropriate. The latter type of infarction is linked with a greater incidence of reinfarction and recurrent ischemia as it usually results from partial occlusion or spontaneous lysis of the thrombus, leaving additional myocardium in danger.

The outcome of infarction, both immediate and long-term is related to the extent and anatomic location of the infarction. Hemodynamic results post-MI depend on the extent of necrosis as well as the presence (or absence) of any previous damage. Cardiac function can range from normal in small infarctions, to failure and hypotension (cardiogenic shock) with more damaging episodes. Collateral circulation and blood flow through a partially

occluded vessel are often responsible for supplying nearby myocardium, placing this tissue at risk. Thus, early management must focus on curbing infarct expansion [5].

4. Developments in Treatment

In 1912 the myocardial infarction syndrome was first related to coronary thrombosis. From that time through the 1940s, the introduction of oral anticoagulant therapy was the only change in treatment--a slow progression. Coronary care units were developed in the late 1950s. In the 1960s direct current defibrillators and closed chest cardiopulmonary resuscitation made a significant impact on the early mortality rate of myocardial infarction. Hemodynamic monitoring of myocardial infarction patients and the recognition that hypovolemia is a correctable cause of shock in some of these patients began in the 1960s as well. The development of counterpulsation minimally improved the survival in patients with pump failure. In the 1970s, greater universal training began in cardiopulmonary resuscitation, as did placement of mobile coronary care units. Pharmacologic methods for preservation of the myocardium were initiated in the 1970s with improvement of myocardial nutrient supply through interstitial diffusion with hyaluronidase or glucose-insulin-potassium solution. Beta-adrenergic blockers and unloading agents were employed as well, to decrease myocardial oxygen requirements [4].

The next major step was with reperfusion through early coronary artery bypass surgery, provided by physicians in Spokane, Washington [6]. Convincing evidence was provided by DeWood et al that the thrombus formed in the coronary artery early in myocardial infarction was likely to spontaneously lyse in some patients over the subsequent hours [7]. Although this surgical approach was not widely adopted due to logistic impracticality, the surgical experiences in Spokane and later Iowa [8] were leaders in reperfusion by surgical thrombectomy and coronary bypass.

Chazov et al. [9] presented data on intracoronary fibrinolysis in acute myocardial infarction in 1976. Rentrop et al. [10] mechanically opened the artery and then used intracoronary thrombolytics to accomplish catheter-directed reperfusion. The era of routine

thrombolysis in patients with acute myocardial infarction began with the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) trial [11] , the first large study of early intravenous thrombolysis. Second generation thrombolytic agents which are more clot specific and third generation agents, possibly represented by a single chain pro-urokinase, may well improve the safety and efficacy of thrombolysis.

C. ACC/AHA Clinical Practice Guidelines: History And Format

In 1980 the American College of Cardiology (ACC) and the American Heart Association (AHA) joined together to form a "Task Force on the Assessment of Diagnostic and Therapeutic Cardiovascular Procedures." The motivating goal was to examine the impact of the vastly expanding technology on the cost and practice of medicine and thus impact the cost of medical care without sacrificing its effectiveness. The ACC/AHA "Guidelines for the Early Management of Patients With Acute Myocardial Infarction" was introduced in 1990 to summarize recent advances and provide guidelines for appropriate patient management following acute MI. Ultimate decisions regarding patient care, however, should be made by the physician and patient according to clinical judgment and individual patient needs [4] .

The ACC/AHA guidelines provide expert opinion and the evidence for a given diagnostic procedure, therapy, or intervention using the following format [1] :

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some ways may be harmful.

D. Treatment Options

1. Thrombolysis

a. Rationale for Thrombolytic Therapy

Complete occlusion may result from rupture of an unstable plaque within a coronary artery. AMI and resulting left ventricular dilation can then occur, potentially

leading to complete heart failure, electrical instability and death. Lysing the clot as soon as possible, either with thrombolysis or primary PTCA, will decrease the extent of left ventricular dysfunction and dilation, lowering the chance of heart failure and harmful arrhythmia. Even reperfusion after 4 to 6 hours have passed has beneficial effects. Such late reperfusion can positively affect infarct healing and decrease remodeling of the left ventricle, systolic dysfunction, and electrical instability [12].

b. General Mechanisms of Action

All thrombolytics to date share some common features. They all act either directly or indirectly to enzymatically convert plasminogen to plasmin which in turn cleaves fibrin thus lysing thrombi. Plasminogen, a single chain molecule is cleaved at the arginine 560-valine 561 location forming plasmin, a double chain molecule and exposing plasmin's its active site. Plasmin can then serve as a serine protease that hydrolyzes fibrin and dissolves the clot [1, 13].

In each case, clot dissolution and subsequent reperfusion occur with a higher frequency when therapy is initiated early after clot formation, since clots become more resistant to lysis as they age. Unfortunately, increased local thrombin may occur as the clot dissolves, leading to enhanced platelet aggregatabiltity and thrombosis. Strategies to prevent this include administration of antiplatelet drugs such as aspirin, or antithrombotics such as heparin.

Differences among thrombolytic agents include their specificity for clot-bound fibrin versus circulating fibrin, their half life, rate of action, bleeding risks and expense. The first agents to be approved, streptokinase and urokinase, cause a systemic fibrinolytic state that can lead to bleeding problems. Alteplase, also known as tissue-type plasminogen activator (tPA), acts more locally on the thrombotic fibrin to produce fibrinolysis, and is a potentially important agent in treating thromboembolic disease. Clinical experience has shown about equal efficacy between streptokinase and tPA. Recent trials have led to a

quicker tPA administration--dose applied over 90 minutes rather than 180--leading to earlier thrombolysis without increased bleeding risk.

The clinical gains that amass from increased patency of the "infarct-related" vessel in those treated with thrombolytic agents include less left ventricular failure, reduction in fatal arrhythmias, a decreased number of serious complications such as septal rupture and cardiogenic shock, and decreased mortality. Several studies following patients for up to five years after thrombolytic therapy reveal improvements in both short and long-term survival. This therapy, however, is still in need of improvement, as rates of in-patient re-occlusion have been reported to be as high as 10%, increasing to 30 % by 3 months. Additionally, re-infarction is a possibility, occurring in up to 5% of in-patients and 7% of thrombolytic-treated patients within the first year [12].

c. Adverse Effects

Bleeding is a major adverse effect of thrombolytic therapy as these agents are equally likely to dissolve the fibrin of a dangerous thrombus as they are to dissolve the fibrin of a much needed hemostatic plug. Occult lesions, such as a peptic ulcer, may bleed subsequent to thrombolytic therapy. Therefore, thrombolytics are contraindicated in patients who have a healing wound, a history of stroke, metastatic cancer, or who are pregnant. After the initial clot is lysed, rethrombosis is possible if thrombogenic stimuli still exist [13].

d. Overview of Clinical Trials

Large, well-designed clinical trials have established that thrombolytics successfully improve outcome post-AMI and positively affect both myocardial salvage and remodeling. An extensive survey of nine trials involving thrombolytic therapy, each trial including more than 1000 patients, was performed by The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group [14]. Cumulative data from the 58,600 enrolled patients revealed that relative to standard medical treatment, thrombolytic therapy offers a highly significant 21% reduction ($p<0.00001$) in 35-day mortality among AMI patients with ST elevation on initial

EKG. This corresponds to an absolute reduction of 21 deaths per 1000 patients treated. In contrast, the patients presenting with ST segment depression had only an 11% reduction in mortality. This excess mortality serves as part of the basis for the perception that thrombolytic therapy does not benefit patients presenting with ST segment depression [1].

Interestingly, the ISIS-2 study [15], the largest of the studies included in the FTT analysis, revealed a 53% reduction in mortality when aspirin and streptokinase were administered together within 4 hours of AMI compared with control (6.4% vs. 13.1%, P=0.0001).

A definite time-dependent effect of thrombolytic therapy on mortality was disclosed in these studies. With regard to the time elapsed from the onset of symptoms until thrombolysis was initiated, 35 lives were saved per 1000 for 0-1 hour, 25 lives per 1000 were saved for 2-3 hours, 19 lives were saved per 1000 for 4-6 hours, and 16 lives were saved per 1000 for 7-12 hours. Thrombolysis administered within 6 hours of symptom onset results in the highest success rates. Collectively these data indicate that benefit exists from thrombolytic therapy if it is initiated within 12 hours from the onset of symptoms [12]. In addition, composite results from two other trials, LATE [16] and EMERAS [17], show that thrombolytics initiated between 6 and 12 hours from the start of ischemic symptoms may still provide a reduction in mortality. Hence, the "window" of treatment with thrombolytics has been defined to be within 12 hours from the onset of ischemic symptoms [1, 12].

e. Recommendations [1, 12]:

Class I

1. ST elevation (greater than 0.1 mV, two or more contiguous leads)[1], time to therapy 12 hours or less[2], age less than 75 years.

---

[1] Repeat ECGs recommended during medical observation in effective clinical settings when initial ECG is nondiagnostic of ST elevation.

[2] Time of symptom onset is defined as the beginning of continuous, persistent discomfort that brought the patient to the hospital.

2. Bundle branch block (obscuring ST-segment analysis) and history suggesting acute MI

Class IIa

1. ST elevation , age 75 years or older.

Class IIb

1. ST elevation , time to therapy greater than 12 to 24 hours .
2. Blood pressure on presentation greater than 180 mm Hg systolic and/or greater than 110 mm Hg diastolic associated with high-risk MI.

Class III

1. ST elevation , time to therapy greater than 24 hours , ischemic pain resolved.
2. ST depression only.

f. Contraindications and Cautions

As mentioned previously, the most substantial risk of thrombolytic therapy is hemorrhage, especially intracranial hemorrhage (ICH), which can be fatal in greater than half to two thirds of patients. The risk of stroke from thrombolytics is strongest within the first day of therapy. Clinical variables to be assessed in the emergency department which predict a higher risk of intracranial hemorrhage include age above 65 years (odds ratio 2.2, 95% CI, 1.4-3.5), body weight below 70 kg (odds ratio 2.1, 95% CI 1.3-3.2), hypertension on presentation (odds ratio 2.0, CI 1.2 to 3.2), and t-PA use (odds ratio 1.6, 95% CI 1.0 -2.5).

g. Summary

In summary, thrombolysis is favorable for all patients, irrespective of age, gender, and the existence of comorbidities such as diabetes mellitus, although the extent of benefit does differ among patient groups. When compared with routine medical therapy in AMI-patients with ST elevation, thrombolytics reduce 35-day mortality by 21%. The effects of thrombolytics are time dependent with the strongest benefits obtained when administered within 6 hours from the onset of ischemic symptoms. Therapy within 12 hours from symptom onset, however, is also beneficial. A slightly elevated risk of intracranial hemorrhage is associated with thrombolysis, generally occurring within the first 24 hours of thrombolytic therapy. Risk factors for ICH include age above 65, body weight below 70 kg, hypertension and tPA therapy [1, 12] .

2. Primary Percutaneous Transluminal Coronary Angioplasty (PTCA)

a. General Considerations

Another option for reperfusion therapy in AMI patients, in place of thrombolysis, is primary PTCA. This procedure begins with the patient undergoing immediate angiography--injection of radioopaque contrast medium followed by radiography of vessels [18]. Primary angiography is accompanied by PTCA which involves dilation of coronary artery stenosis by balloon inflation under high pressure. This procedure should be done as soon as possible, for using a guidewire and balloon to traverse a complete occlusion caused by recent thrombus is much easier than trying to cross a hardened, well- established one. Atheromatous plaque is ruptured and intraluminal debris resorbed. The patient is given local anesthesia and the procedure is carried out in the cardiac catheterization laboratory at the time of diagnostic arteriography or later.

When wire guided balloon angioplasty is used for reperfusion in place of thrombolytics this is called "direct or primary angioplasty." Other applications of PTCA include its use as an adjunct to thrombolysis or for management of patients who did not receive thrombolytics and are now in the subacute stage (2-7 days) post MI. "Rescue" PTCA may be performed right away if thrombolytics were not successful or if the patient has a extreme stenosis in the infarct-related vessel. Strategies have been mentioned for people with residual stenosis > 70% following thrombolysis to have "immediate" PTCA--within a few hours, or "deferred"--within the next seven days. "Elective" PTCA is another approach in which an AMI patient, independent of previous thrombolytic therapy, undergoes angioplasty because of exercise induced or spontaneous ischemia [12].

The best lesions for PTCA are relatively proximal, noneccentric, without major calcification or plaque dissection, and not at the origin of large branches. The main early complication of this procedure is intimal dissection and vessel blockage. If this occurs, repeat PTCA or placement of an intracoronary stent can resolve the situation. In 1-2% of cases, CABG is required and therefore must be available in a center performing PTCA.

Restenosis, although susceptible to treatment with repeat PTCA is the major limitation to this method, occurring in 30-40% of vessels dilated after the first 6 months.

Intracoronary stent placement seemingly reduces the incidence of restenosis. At first, aggressive anticoagulation was used following stent placement to avoid the small risk of acute thrombosis. However, the present regimen, including high pressure balloons and intravascular ultrasound for placement followed by antiplatelet therapy with aspirin and ticlopid has lead to an acute thrombosis rate of below 1%. Stents are currently used in greater than 30% of PTCA procedures in the US [5] .

While the ensuing discussion will focus on the use of primary PTCA, secondary PTCA plays an important role in post-MI treatment as well. Although some physicians will perform angiography and PTCA on all patients following AMI, present data show that this routine will not salvage myocardium or reduce the likelihood of reinfarction or death. Instead, this management strategy should be reserved for patients who have had an AMI and now have good left ventricular (LV) function but spontaneous or provoked ischemia [1] . Additionally, acute catheterization and PTCA or CABG is appropriate in patients with cardiogenic shock and in patients with hemodynamic compromise (systolic blood pressure > 100 mm Hg [5] .

b. Overview Of Clinical Trials

Meyer et al [19] , in 1982, were first to publish data on the use of primary PTCA rather than thrombolysis in AMI patients. Since then the issue has been the source of much debate. Being that there are no randomized clinical trials comparing direct PTCA to no reperfusion, recommendations are based on indirect evidence and on medium-sized trials that compare thrombolysis vs. PTCA.

Initially, it was shown that greater than 90% of the time, PTCA successfully restored forward flow in the "infarct-related" vessel and had a 90-96% 1-year survival rate. In subsequent studies comparing PTCA to thrombolysis, post -AMI, PTCA restored forward flow about 88-95% of the time [1] . Using angiography several weeks after MI,

Zijlstra et al [20] , in 1993, showed that patients who had been treated with PTCA had a 91% rate of having a patent "infarct-related" artery while those who had undergone thrombolysis had only a 68% patency rate (P=.001). Stenosis was also greater in the thrombolytic patients. Adverse in-hospital outcomes such as nonfatal infarction, recurrent ischemia, the need for coronary revascularization, and death were decreased among PTCA treated patients.

A meta-analysis proposes that PTCA, as compared to thrombolysis, will reduce the probability of recurrent ischemia and thereby reduce ensuing hospital morbidity, hospitalization and expenses [21] . This advantage, however, is in exchange for performing PTCA on all patients post MI (rather than just the 20% to 40% who actually need recanalization following thrombolysis).

c. Limitations

Despite the above evidence that PTCA may be preferable to thrombolysis in post-AMI treatment, it is important to consider that only 20% of United States hospitals have the necessary catheterization equipment, and even less have the ability to do emergency PTCA. The time delay that would be involved in transferring a patient to a facility that does have the aforementioned capabilities may outweigh the benefits of PTCA.

In addition, the superb results obtained in clinical trials with the use of PTCA may not be reproducible in the community, as the physicians involved in these studies have been exceptionally experienced in performing PTCA and dedicated to adhering to the protocol with every step. Additionally, time was not a limiting factor in these studies as PTCA was performed within 60-90 minutes from patient arrival (the recommended time frame being that balloon dilation should occur within 60-90 minutes of AMI diagnosis). In recent community-based registries in the United States and Europe the time elapsed between patient arrival to the hospital and PTCA had been greater than the time needed until thrombolytic infusion. These registries show a similar in-hospital mortality for patients treated with both therapies.

In addition to the issue of institution capability and time delay, 2%-5% of patients who undergo PTCA will require emergency CABG, either because of an artery that was not appropriate for PTCA or because failed angioplasty dictates further surgical treatment. Thus PTCA can only be performed in hospitals with CABG capabilities or definite plans for immediate access to another facility with this proficiency [1].

d. Recommendations [1]:

Class I

1. As an alternative to thrombolytic therapy only if performed in a timely fashion by individuals skilled in the procedure[3] and supported by experienced personnel in high-volume centers[4].

Class IIa

1. As a reperfusion strategy in patients who are candidates for reperfusion but who have a risk of bleeding contraindication to thrombolytic therapy.
2. Patients in cardiogenic shock

Class IIb

1. As a reperfusion strategy in patients who fail to qualify for thrombolytic therapy for reasons other than a risk of bleeding contraindication.

e. Summary

Primary PTCA is a good alternative to thrombolytic therapy if the timing is right and appropriately skilled personnel are available. Additionally, one should be certain of direct availability of emergency CABG surgery before engaging in primary PTCA [1].

3. Coronary Artery Bypass Graft Surgery (CABG)

a. General Considerations

The technique of surgical revascularization by CABG includes establishing vascular grafts and bypassing the occlusion. Grafts using one or both internal mammary arteries, generally to the left anterior descending artery or its branches, lead to the best long term patency and flow results. One can also create a graft connecting a segment of the saphenous (or, less favorably, other veins) from the aorta to the occluded coronary artery, distal to the area of obstruction. One to five distal anastomoses are common [5]. In patients who require revascularization within 48-72 hours post AMI, PTCA is still the

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[3] Individuals who perform more than 75 PTCA procedures per year.
[4] Centers that perform more than 200 PTCA procedures per year.

preferable method. Surgery, however is indicated in the patient who was unsuccessfully treated with PTCA or who has the high risk coronary anatomy appropriate for CABG--stenosis of the left main coronary artery (above 50%), three vessel disease, disease in two vessels plus involvement of the left anterior descending artery proximally, disease in two vessels that is not appropriate for PTCA, and decreased ejection fraction. left main coronary artery disease or expansive, multivessel involvement.

Patients with the appropriate anatomy show an increased long-term survival from elective CABG following MI. Retrospective studies suggest that if CABG is performed 3-7 days following MI, mortality is similar to that of other elective CABG procedures. The operative risk is increased in patients with emergency surgery, increased age and reduced ventricular function.

The majority of patients who undergo CABG following AMI--about 10-20 % of AMI patients-- undergo the procedure due to chest pain that will not remit or is recurrent despite thrombolysis or PTCA, the appropriate coronary anatomy revealed by catheterization, or a complication following AMI such as papillary muscle dysfunction leading to severe mitral regurgitation or ventricular septal rupture. Severe hemodynamic and ischemic instability that persists following AMI also dictates a situation in which the patient should have surgical revascularization.

Emergency cardiac surgery in AMI carries an approximately 2% in-hospital and 25% 10-year mortality rate in certain centers. This success is due to advanced surgical techniques and enhancement in cardioplegia and hypothermia mechanisms resulting in greater cardiac preservation during bypass surgery. Similar to other methods intended to impede further infarct, myocardial salvage is most efficient if the surgery is performed within the first 4-6 hours following onset of AMI. However, given the amount of time that is feasibly required to carry out the various steps needed from the time an out-patient experiences symptoms to the time one can operate, it is not likely that this will become a standard method of treatment. In fact, operating on a patient with an uncomplicated Q-

wave infarct more than six hours after onset has been shown to increase hemorrhage to the infarct area and is thus contraindicated in this scenario. The only group that may benefit from CABG greater than six hours after onset of AMI are patients, including those in cardiogenic shock, in whom the infarct occurs in a stunning fashion (i.e., over several days). This benefit, however, has not been definitively established.

Emergency operation in a patient with active and persistent ischemia or cardiogenic shock increases the operative mortality. Surgeries , however, that take place more than 24 hours after AMI in patients who have had successful thrombolysis but still have stenosis and are anatomically more suitable for CABG than PTCA have a mortality rate of about 4%. Autopsy studies have found that hemorrhagic necrosis is extensive in these patients. If a patient has had thrombolysis within the last 6-12 hours and now requires CABG, the patient's coagulation system must be repleted with aprotinin and fresh-frozen plasma. There is an increase in minor bleeding and postoperative chest tube drainage following emergency CABG relative to an elective procedure but these do not represent a primary area of concern [12] .

b. Recommendations for Emergency or Urgent CABG [1] :

Class I
1. Failed angioplasty with persistent pain or hemodynamic instability in patients with coronary anatomy suitable for surgery.
2. Acute MI with persistent or recurrent ischemia refractory to medical therapy in patients with coronary anatomy suitable for surgery who are not candidates for catheter intervention.
3. At the time of surgical repair of postinfarction VSD or mitral valve insufficiency.

Class IIa
1. Cardiogenic shock with coronary anatomy suitable for surgery.

Class IIb
1. Failed PTCA and small area of myocardium at risk; hemodynamically stable.

Class III
1. When the expected surgical mortality rate equals or exceeds the mortality rate associated with appropriate medical therapy.

c. Summary

In summary, prior to the successful development of thrombolytic agents and PTCA for coronary reperfusion, studies that compared AMI patients treated with CABG vs. controls indicated that emergency CABG patients had a better chance of living longer and a higher percentage of rescued myocardial tissue. Given the surgical nature of this procedure, CABG use is mostly in situations where other therapies have been unsuccessful or inadvisable in AMI patients. Overall, there are four situations where immediate surgical intervention is advised: (1) the patient had unsuccessful PTCA and now suffers from persistent chest pain or hemodynamic instability; (2) the patient that is not a candidate for catheterization but has persistent or recurrent ischemia that is refractory to medical management; (3) the patient who is in cardiogenic shock but can't undergo PTCA because of unsuitable anatomy; and (4) the patient with a mechanical dysfunction[5] causing severe pulmonary congestion or hypotension should also have surgical intervention [1].

. E. Rationale and Approach to Pharmacotherapy

1. Nitroglycerin

a. General considerations and Mechanism of Action

Organic nitrates (and nitrites) are simple nitric and nitrous esters of alcohols. They all rapidly reduce myocardial oxygen demand and thus rapidly relieve symptoms. Nitrates, beta-blockers and calcium channel blockers are all appropriate for use to relieve anginal pain. However, nitroglycerin, sublingual or spray form, is the drug of choice for prompt relief of an anginal attack brought on by exercise or emotional stress.

The principal action of nitrates is vasodilation, mostly via inducing relaxation of vascular smooth muscle in veins, arteries, and arterioles. Nitroglycerin and other organic nitrates convert to nitrite ions intracellularly. They then convert to nitric oxide (NO) which in turn activates guanylate cyclase and raises the amount of cyclic GMP within the cell. Elevated cGMP leads to dephosphorylation of the myosin light chain and ultimately results

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[5] Examples include a papially mucsle rupture causing mitral regurgitation or a ventricular septal defect.

in relaxation of vascular smooth muscle [13]. Nitric oxide, also known as endothelium-derived relaxing factor (EDRF), is an important modulator of vascular tone which is endogenously produced. In patients with coronary artery atherosclerosis, however, it is believed that endogenous stores are depleted and thus exogenous administration in the forms of nitrates is needed [1].

Nitroglycerin decreases cardiac work and thereby decreases myocardial oxygen demand. At therapeutic doses its two major effects include the dilation of the coronary bed and the dilation of large veins, especially in the splanchnic and mesenteric circulations, causing pooling of blood in the veins. The former action increases blood supply to the myocardial tissue while the latter action diminishes venous return of blood to the heart (preload) and therefore reduces the work of the heart [13]. Nitroglycerin will also decrease afterload by causing arterial vasodilation. The combined decrease in right and left ventricular preload as well as afterload reduction greatly decreases the work of the heart and reduces oxygen demand. Myocardial ischemia is relieved as the ratio of myocardial oxygen demand to myocardial oxygen supply decreases. Patients with impaired LV systolic function or CHF especially benefit from nitrates. Additionally, nitrates increase the subendocardial-epicardial blood flow ratio by not only causing direct vasodilation of the coronary vasculature but also by inducing prevention of occasional vasoconstriction of coronary arteries. Some atherosclerotic lesions which have intact vascular smooth muscle are widened, increasing the caliber of arterial openings and increasing flow. Other actions of nitrates include their ability to dilate coronary collateral vessels, decrease the vasoconstriction of small coronary arteries distal to the point of obstruction and lower platelet aggregation [1].

b. Limitations and Adverse Effects

Headache is the most common adverse effect of nitroglycerin and other nitrates, occurring in 30-60% of patients receiving nitrate therapy with long acting agents [13]. In addition, nitroglycerin can increase ventilation-perfusion mismatch and thereby exacerbate

hypoxemia. The most worrisome side effect is unintentional systemic hypotension leading to reflex tachycardia and aggravation of an already ischemic myocardium. Patients with inferior wall MI, frequently associated with RV infarction, are reliant on RV preload for adequate cardiac output and would be especially susceptible to extreme hypotension from nitroglycerin. Should bradycardia and hypotension result from nitroglycerin use, one should discontinue the drug, elevate the patient's legs, rapidly provide fluids and administer atropine.

The greatest limitation to nitrate therapy is the tolerance that the body develops to its anti-ischemic actions with continued use. The body rapidly loses sensitivity to the actions of nitrates and requires a drug-free interval in order to restore previous sensitivity. The reason for tolerance is not certain although several etiologies have been proposed. One possibility is that the body depletes certain sulfhydryl groups required to convert organic nitrates to nitric oxide. A recent suggestion is that increased production of superoxides by the vasculature may be responsible. Continuous infusion of intravenous nitroglycerin for 24-48 hours following acute MI should not cause tolerance. If tolerance is evident, the dose can be increased [1]. Nitroglycerin patches, in contrast, are worn for 12 hours and removed for 12 hours [13].

An important drug interaction to be aware of is the decreased sensitivity to heparin that occurs when one is taking nitroglycerin and heparin simultaneously. This is important to recognize, as one might require an increased dose of heparin to maintain effectiveness if nitroglycerin is also administered. Likewise, the patient is at a greater risk of bleeding from the heparin dose when nitroglycerin is discontinued.

c. Overview of Clinical Trials

In addition to its anti-ischemic effects, experimental and clinical evidence suggests that nitroglycerin will also limit infarct size, improve function in the infarcted region, and decrease LV remodeling that may occur following a Q-wave MI. An improvement in mortality and cardiac morbidity following prompt IV nitroglycerin use has also been shown

[1]. A meta analysis indicated that nitroglycerin decreased the odds of mortality from acute MI by 35% (95% CI, 28-49%; p<0.001) [22].

The GISSI-3 trial [23] and the ISIS-4 trial [24] are two large trials that examined the effects of nitrates in the context of thrombolytic and aspirin therapy with a primary end point of short-term mortality. In these trials and when all data are compiled from the various randomized controlled trials involving nitrate therapy in AMI, there is a small, statistically significant relative reduction in mortality (5.5%+/-2.6%; p=0.03) which corresponds to saving about 4 lives for every 1000 persons treated.

d. Summary

In summary, nitroglycerin is the drug of choice for periodic ischemic pain and is effective at decreasing blood pressure and alleviating pulmonary congestion. Although there is no definitive data, a patient with an AMI and without bradycardia, excessive tachycardia, or hypotension should be treated with intravenous nitroglycerin for the first 24-48 hours after hospitalization. Intravenous infusion enables a rapid onset of action, easy dosing control with frequent heart rate and cuff blood pressure measurement, and the ability to quickly end treatment rapidly should unwanted effects occur. Intravenous nitroglycerin should also be administered to manage patients with CHF or hypertension. Patients with CHF and large Q-wave infarcts should continue treatment with oral or topical preparations. However, since no increase in outcome was observed in the ISIS-4 or GISSI-3 trials, when over 70,000 patients were followed on nitrates versus placebo, or when all relevant randomized controlled trials are analyzed together, it is clear that routine administration of nitrates for long-term treatment of uncomplicated AMI is not recommended [1].

2. Aspirin and Other Platelet-Active Drugs

a. Mechanism of Action

Since platelets and thrombus formation are key factors in pathogenesis of ischemia and infarction, antiplatelet agents should, intuitively play a crucial role in medical management of occlusive cardiovascular disease.

Aspirin is a weak organic acid that irreversibly acetylates, and thus inactivates, cyclooxygenase. Since cyclooxygenase is a key enzyme in the synthesis of prostaglandin and thromboxane A2 from arachiodonic acid, aspirin can irreversibly inhibit thromboxane synthesis in platelets. The inhibition is permanent for the 7-10 day life time of the platelet, as platelets lack a nucleus and thus cannot synthesize new cyclooxygenase. Being that thromboxane A2 is necessary to induce platelet aggregation, aspirin treatment irreversibly suppresses platelet aggregation, the initial step in thrombus formation [13]. Aspirin will also affect platelets through its actions on vascular endothelial cells. In these cells aspirin inhibits the production of prostacyclin, an inhibitor of platelet aggregation. This effect, however, is short-lived as vascular endothelial cells do contain nuclei and can generate new cyclooxygenase in response to aspirin therapy.

b. Prevention of Thrombotic Complications of Atherosclerosis

The Antiplatelet Trialists' Collaboration, which included 145 trials using antiplatelet therapy (mostly aspirin), revealed that antiplatelet therapy is effective in preventing vascular events in patients with AMI, history of MI, history of stroke or cerebral ischemia, unstable angina, and other vascular diseases. All together, nonfatal MI, nonfatal stroke, and vascular death were reduced by 30%, 30%, and 17%, respectively, in high-risk patients. Aspirin has been found to be more beneficial in patients with a vascular history, preventing 35 and 40 events per 1000 treated patients with a history of infarction or stroke, and preventing 4 events per 1000 asymptomatic men treated.

c. Side Effects

When aspirin is used as secondary prevention in patients with coronary artery disease, it clearly reduces the risk of stoke. However, when studied in primary prevention trials, in patients without atherosclerotic disease, aspirin is associated with a small raise in stroke rates. It is speculated that perhaps its antihemostatic effect, which may slightly increase the healthy patient's risk of cerebral hemorrhage, is offset in the patient with coronary artery disease by its beneficial decrease of thromboembolic stroke [1].

The other main adverse effects of aspirin relate to its gastrointestinal actions. As mentioned previously, aspirin blocks the production of prostaglandins and thromboxane A2. In the gastrointestinal system, however, these prostaglandins play an important, protective role; prostacyclin (PGI2) inhibits production of gastric acid while PGE2 and PGF2 alpha stimulate the production of mucus that protects the lining of the stomach and small intestine. When aspirin is ingested and these prostanoids are not synthesized, there is an increase in gastric acid secretion and a decrease in mucous protection, predisposing the patient to epigastric pain, ulceration, and/or hemorrhage [13]. These side effects can be limited by diluting the aspirin solution, using enteric coated aspirin or treating the patient with cimetidine or antacids. Rectal suppositories can be used in the patient with a bleeding history from peptic ulcers.

Aspirin should not be used in patients with known hypersensitivity and should be prudently administered to the patient with blood dyscrasia or liver failure. Another harmful effect associated with aspirin use is bleeding from surgical cuts [1]. In the Veterans Administration Cooperative Study [25], 6.5% of patients given aspirin and 1.7% of patients not receiving aspirin ($P<.01$) had significantly greater post-operative chest drainage and further surgery because of hemorrhage. Other studies have similarly found an increased amount of post-operative chest drainage in patients that had been on aspirin, but did not find an association with the need for reoperation [26, 27]. A solution found in another Veterans Administration Cooperative Study [28] is that if patients begin aspirin

therapy 6 hours after surgery, as opposed to prior to surgery, its anti-thrombotic effects on the saphenous vein bypass graft are still intact , and yet it is not associated with increased bleeding from surgical sites.

d. Ticlopidine

Ticlopidine inhibits platelet aggregation, as does aspirin, but uses a distinct mechanism. This drug targets the ADP pathway involved in platelet binding to fibrinogen and to each other. Part of its action involves blocking the GPIIb/IIIa glyocoprotein receptor on the platelet membrane that binds fibrinogen. This drug is not used for emergency anti-platelet activity, as its onset of action begins 24-48 hours after administration.

This agent has been found to decrease the incidence of thrombotic stroke and reduce the occurrence of AMI in patients with vascular pathology. A serious adverse effect of ticlopidine therapy, however, is neutropenia which is reversible and has occurred following treatment of greater than 2 weeks. Hence, ticlopidine administration is reserved for patients with cerebral ischemia who cannot tolerate aspirin, have been treated unsuccessfully with aspirin, or have contraindications to its use [1, 13] .

3. Antithrombotics/Anticoagulants

a. Coagulation System

The coagulation system is essentially a pathway of conversions of proenzymes to enzymes, finishing off in the polymerization of fibrinogen to fibrin. The intrinsic and extrinsic parts of the clotting cascade converge with the activation of factor X. Activated factors X and V and phospholipid are then necessary for the conversion of prothrombin to thrombin and thrombin is then essential for the ultimate conversion of fibrinogen to fibrin. There are many control mechanisms to avoid the unchecked spread of coagulation. In the presence of fibrinogen and fibronectin, thrombin induces the endothelial cell to liberate urokinase and tissue-type plasminogen activators (tPA) to convert plasminogen to plasmin, an enzyme

which solubilizes fibrin and dissolves blood clots. Among the several other mechanisms of checks and balances used by the body to control coagulation is the role of antithrombin III. This molecule, in the presence of heparin-like molecules on endothelial cells inhibits thrombin and reduces the activity of factors XIIa, Xia, Xa, and IXa-- essential enzymes of the intrinsic pathway [29].

One therapeutic angle in preventing thrombus formation is to target thrombin and thereby inhibit fibrin formation from fibrinogen. Not only is thrombin a key component of initial thrombus formation, but it also is important in activating platelets. Additionally, upon exposure to the circulating blood, active thrombin that is bound to a developing clot will further convert fibrinogen to fibrin. Hence, inhibiting the action of thrombin is a potent way to curb clot formation.

b. Heparin

1. Mechanism of Action

The pharmacologic agent heparin, first described in 1916, is a mixture of straight-chain anionic glycosaminoglycans of different sizes, with molecular weights ranging between 5000 to 20000. The different sized molecules exert distinct effects on the coagulation system, overall leading to a rapid anticoagulant effect with maximal anticoagulation taking place within minutes after intravenous injection of heparin. Heparin binds to antithrombin III causing a conformational change that enables antithrombin III to combine with and inactivate thrombin that is not already bound to fibrin[6]. Additionally, the heparin-AT-III complex can inactivate activated factor X.

The effect of a heparin dose on the coagulation system can be adjusted in several ways, including the specific combination of heparin molecules administered, blood levels of AT-III, plasma levels of proteins that inactivate thrombin such as platelet factor IV, and the capability of heparin to effect thrombin bound to clot.

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[6] The complex of heparin and AT-III is considerably large and generally not effective against thrombin bound to clot.

2. Overview of clinical trials

In this age of aspirin, beta-blockers, nitrates and ACE inhibitors, there are few studies that have formally evaluated the efficacy of heparin among patients not receiving thrombolytic therapy. However, there are useful data from studies performed before the emergence of thrombolytic therapy which serve as the basis for the recommendation to administer heparin to patients not receiving thrombolytic therapy. In these trials the control groups were not treated with the routine therapies of today, such as aspirin [1]. An overview of these studies reveals that a 17% decrease in mortality and a 22% decrease in reinfarction risk occurred when heparin was administered [30].

Recommendations for heparin therapy in patients receiving thrombolytic therapy depend on the type of thrombolytic used. Thrombolytic agents that are nonspecific such as streptokinase, anistreplase, and urikinase require less additional anticoagulation. For, these agents cause an overall disruption of the coagulation system, including consuming factors V and VIII and engendering vast amounts of fibrin degradation products, which themselves serve as anticoagulants. In contrast, agents such as alteplase and reteplase may not produce many fibrinogen degradation products or consume many coagulation factors. These agents would require greater anticoagulation effects from heparin.

Overall, clinical trials do not support the use of intravenous heparin with a nonspecific thrombolytic versus subcutaneous heparin with the thrombolytic. Additionally it is unclear whether subcutaneous heparin is beneficial.

Heparin is, however, clearly recommended in the patient with a high risk for embolic stroke[7]. Empirical evidence suggests that early heparin administration to the MI patient will reduce the likelihood of systemic emboli [1]. In the SCATI trial [31] patients randomly assigned to heparin therapy showed an in-patient mortality of 4.6% compared to

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[7] This group of patients includes those with AF, a prior history of embolism, echocardiographic evidence of a left ventricluar thrombus and a large, anterior MI.

8.85% in the placebo treated group along with a decrease in stroke rate in the heparin-treated group.

3. Recommendations [1]:

Class I
1. Patients undergoing percutaneous or surgical revascularization
Class IIa
1. Intravenously in patients undergoing reperfusion therapy with alteplase.
2. Subcutaneously (7500 U twice daily) (intravenous heparin is an acceptable alternative) in all patients not treated with thrombolytic therapy who do not have a contraindication to heparin. In patients who are at high risk for systemic emboli (large or anterior MI, AF, previous embolus, or known LV thrombus), intravenous heparin is preferred.
3. Intravenously in patients treated with nonselective thrombolytic agents (streptokinase, antistreplase, urokinase) who are at high risk for systemic emboli (large or anterior MI, AF, previous embolus, or known LV thrombus).
Class IIb
1. Patients treated with nonselective thrombolytic agents, not at high risk, subcutaneous heparin, 7500 U to 12500 U twice a day until completely ambulatory
Class III
1.Routine intravenous heparin within 6 hours to patients receiving a nonselective fibrinolytic agent (streptokinase, anistreplase, urokinase) who are not at high risk for systemic embolism.

4. Antiarrhythmic drugs

a. Introduction to Arrhythmia

Arrhythmia is a frequent problem in post-infarction patients, occurring in over 80% of patients with AMI. Approximately 5% of hospitalized patients post AMI will develop ventricular fibrillation, as cardiac output is impaired and tachycardia may deteriorate into ventricular fibrillation. Of these episodes, 80% occur in the first 12-24 hours [5].

Cardiac arrhythmias consist of depolarizations that result from disturbances in impulse formation, disturbances in impulse conduction or both [13]. These aberrant impulses have a site of origin, rate, regularity, or conduction that is abnormal. Arrhythmias can cause contractions that are too rapid, too slow or asynchronous and thus provide inadequate cardiac output. More serious, even lethal rhythm disturbances may result including ventricular fibrillation which may develop from early premature ventricular depolarizations.

b. General Mechanism of Antiarrhythmic Therapy

Since arrhythmias result from aberrant pacemaker activity or deviant impulse propagation, the goal of antiarrhythmic therapy is to limit ectopic pacemaker activity and change conduction or refractoriness in reentrant circuits to impair circus movements. The primary methods by which this can be accomplished include targeting the action potential of myocytes by blocking sodium channels, blocking sympathetic autonomic effects in the heart, prolonging the effective refractory period, or blocking calcium channels.

Antiarrhythmic drugs have greater effects on abnormal tissue than normal tissue. They will decrease the automaticity of ectopic pacemakers more than that of the sinoatrial node. Also, they reduce conduction and excitability and increase refractory period to a greater extent in depolarized tissue than in normally polarized tissue, mainly by selectively blocking the sodium or calcium channels of depolarized cells.

c. Adverse Effects

In patients with arrhythmias treatment with antiarrhythmic drugs can save the patient's life. In other instances, however, the hazards of antiarrhythmic therapy which include inducing lethal arrhythmias in certain instances, may outweigh the potential benefits of treatment [32]. Examples of drugs that are beneficial to use and result in decreased morbidity include the use of lidocaine to terminate ventricular tachycardia or adenosine or verapamil for supraventricular tachycardia [13]. In contrast, many other agents are known to be proarrhythmic and would not be useful [32].

The Cardiac Arrhythmia Suppression Trial (CAST) showed that the two class IC antiarrhythmic drugs, encainide and flecainide, did prevent ectopic ventricular beats in post MI patients. However, if either drug continued to be used, a two- to three-fold increase in death due to arrhythmias resulted. Unexpectedly, this trial challenges the seemingly logical thought that treating post-infarction arrhythmias, or any arrhythmia in general, is beneficial, causing physicians to be more skeptical in the use of antiarrhythmics [13]. In general, it is

now established that due to the proarrhythmic risk of antiarrhythmic therapy, asymptomatic or minimally symptomatic arrhythmias should not be treated.

d. Specific Agents and Recommendations

1. Lidocaine

Lidocaine is both an antiarrhythmic and local anesthetic that targets sodium channels with relatively rapid onset [1]. Randomized studies revealed that lidocaine decreases risk of primary VF in both the prehospital and early hospital environment [33, 34]. Nevertheless, deaths relating to asystole and electromechanical dissociation occur, resulting in no overall mortality decrease.

Following AMI, treatment is advised for premature ventricular complexes, VT or VF. In this setting, lidocaine is the drug of choice. Except for patients in shock, it is well sustained [1]. According to the 1996 ACLS protocol [35], lidocaine is the first antiarrhythmic agent to be administered to patients who have had a cardiac arrest with persistent VT/VF even after defibrillation and epinephrine. It is also recommended for cardiac arrest patients to ward off recurrence, as therapy for unsustained ventricular ectopy, and as treatment for wide complex tachycardia of undetermined type.

2. Bretylium

Bretylium is a quaternary ammonium compound that has been shown, clinically and experimentally , to have strong antifibrillatory but weak antiarrhythmic effects. It is used to treat resistant VT and VT in the hemodynamically unstable patient. It is recommended in the ACLS protocol to be used after lidocaine and previous steps have been unsuccessful against VF or pulseless VT or when VF recurs despite epinephrine and lidocaine use. In patients with VT and with a pulse, it is used only once treatments with lidocaine and procainamide have been attempted.

3. Procainamide

Procainamide is an antiarrhythmic that works on sodium channels and also has local anesthetic properties. It is used as a secondary agent in life threatening ventricular

arrhythmias. When therapy is needed to suppress premature ventricular complexes and recurrent VT, after lidocaine use has either failed or is contraindicated, procainamide can be administered. It can also be used as a secondary agent for wide complex tachycardias of undetermined type. According to ACLS guidelines, procainamide should be considered after defibrillation, epinephrine, lidocaine, bretylium, and magnesium have failed to treat VF and VT without a pulse. Side effects of procainamide use involve arrhythmias including torsades de pointes. Renal failure patients may accumulate metabolites and be at higher risk for torsades [1].

4. Beta-adrenoceptor Blockers

Traditionally, beta-blockers, class II antiarrhythmic agents, have been considered relatively poor agents for the treatment of ventricular arrhythmias. However, recently there has been convincing evidence that beta-blockers have important antiarrhythmic actions, serving to prevent arrhythmic and sudden death. Specifically, B blockade may prevent sudden death and VF, but is less effective against spontaneous ectopy or spontaneous or inducible monomorphic VT. The antiarrhythmic effects of beta-blockade may be due to an intrinsic action of these drugs, an affect on the central nervous system, and preservation of the antiarrhythmic action of other agents amidst sympathetic stimulation.

A specific role for beta-blockade in antiarrhythmic therapy is still evolving. Recent studies do show that agents with class III effects and beta-blockade are superior to class I or purely class II agents in treating high-risk populations. Although still unproved, beta-blockade is a reasonable therapy for patients who have not had cardiopulmonary arrest and are at high risk for VF. Beta-blockade, alone, in treatment of patients who have suffered a cardiopulmonary arrest or who have sustained VT is unproved, but possibly beneficial. Overall, beta-blockers have the greatest effect on survival in patients with decreased left ventricular function and treatment that involves the use of this class of drugs should be promoted, not avoided [36].

5.Amiodarone

Amiodarone is an antiarrhythmic with a vast, complex array of actions. Intravenous amiodarone is appropriate for prophylaxis against and treatment of recurring VF and hemodynamically destabilizing VT. Long term therapy with oral amiodarone can be used if the intravenous dose is effective. Studies have shown the time to first VT/VF recurrence in patients treated with amiodarone is dose-dependent , although mortality is not [37] . This drug is equal to bretylium in effectiveness against VT/VF recurrence but is better tolerated [38] .

e. Summary

Prophylactic antiarrhythmic therapy in the first 24 hours after acute MI is not recommended. Although lidocaine prophylaxis can prevent arrhythmias in AMI patients, it does not decrease mortality and does increase risk for asystole. Thus, this approach is only advised in patients with frequent ectopy or unsustained ventricular tachycardia. Although intravenous magnesium sulfate proved useful in one study, ISIS-4 did not find routine magnesium administration advantageous. Nonetheless, atropine, lidocaine, a transvenous pacemaker or transcutaneous pacing patches, a defibrillator and epinephrine should be directly accessible for the post AMI patient [1, 5] .

The treatment of a patient with arrhythmia following AMI is situation dependent. Extensive left ventricular systolic dysfunction is frequently the cause of atrial fibrillation in the post- MI patients. Should this cause persistent ischemia or compromise the patient's hemodynamic function, direct-current cardioversion is recommended. However, if these comorbidities are not present, beta-blockers or digitalis should be used to slow the arrhythmia. Ventricular fibrillation or monomorphic ventricular tachycardia along with chest pain, hypotension or pulmonary congestion should be treated with direct-current countershock. Monomorphic ventricular tachycardia that is not associated with angina, hypotension or pulmonary congestion should receive antiarrhythmic therapy-- intravenous lidocaine, procainamide or amiodarone.

In general, post AMI patients should only receive both acute or long term antiarrhythmic therapy (except beta-blockers) for life-threatening arrhythmias or those with extensive symptoms. Antiarrhythmic therapy is not appropriate for risk reduction in response to arrhythmias that are not life-threatening [1] .

5. Beta-Adrenoceptor Blocking Agents

a. General Considerations

All the clinically approved beta-blockers are competitive antagonists of catecholamines and other beta agonists at beta-adrenoceptors. Nonselective beta-blockers bind to both beta-1 and beta-2 receptors , whereas cardioselective beta-blockers principally bind at beta-1 receptors. These drugs also vary in intrinsic sympathomimetic activity, central nervous system (CNS) effects, and in pharmacokinetics. Although all beta-blockers reduce blood pressure in hypertension, they do not prompt postural hypotension, as the alpha-adrenoceptors are not antagonized and still maintain usual sympathetic control of the vasculature. Beta-blockers are also beneficial in managing angina, cardiac arrhythmias, MI, and glaucoma, as well as helping to prophylax against migraine headaches.

b. Coronary Effects

In general, beta-blockers have prominent effects on the heart. As one might expect from the role of adrenoceptors in cardiac regulation, antagonism of the receptors by beta-blockers will have negative chronotropic and inotropic effects, resulting in a decrease in cardiac output. They directly lower sino-auricular and atrioventricular activity, decreasing heart rate. The resulting bradycardia is generally dose-limiting [13] . Slowed conduction through the atrioventricular node and an increased PR interval is a result of adrenoreceptor blockade in the atrioventricular node. Cardiac output, work, and oxygen consumption are decreased by blockade of beta-1 receptors, useful effects in the treatment of angina. The beta-blockers are successful in attenuating supraventricular cardiac arrhythmias but are generally not beneficial against ventricular arrhythmias (beside those prompted by exercise). Additionally, beta-blockers oppose the release of renin stimulated by the

sympathetic nervous system. This may in part be responsible for its lowering effects on blood pressure [13, 32] .

Beta blockers have a protective effect on the myocardium. Thus, prophylaxis with beta-blockers will protect patients with a history of myocardial infarction from experiencing another infarct. In addition, beta-blocker administration immediately following an MI will decrease infarct size and quicken recovery . One potential mechanism may be the blocking of the effects of circulating catecholamines, which would augment oxygen demand in an already ischemic heart muscle. Certain beta-blockers like propanolol also reduce the incidence of sudden arrhythmia after myocardial infarction [13] .

c. Adverse Effects

While the above effects are beneficial in some, they are hazardous to others and thus should not be used in those with contraindications. Bronchoconstriction, arrhythmias, sexual impairment, disturbance in metabolism and drug interactions are common side effects of beta-blocker use. Central nervous system effects include sleep disturbances, sedation, and depression. The respiratory effects are important to consider in the asthmatic patient, as nonselective beta-blockers can worsen asthma or other forms of airway obstruction causing a once trivial condition to be a severe handicap. Additionally, since beta-blockers lower the sympathetic drive of the heart, patients with abnormal myocardial function may decompensate from beta-blocker therapy and may not be able to handle the ensuing decrease in myocardial contractility and excitability [13, 32] .

d. Overview of Clinical Trials

Beta-blockers have been shown to decrease morbidity and mortality in post MI patients whether they are taken in the early hours of infarction or weeks, months, or years later as a form of secondary prevention.

Beta-blockers administered to a patient in the beginning hours of infarction can decrease the size of infarction and concomitant complications in the patient not receiving thrombolytic therapy as well as decrease the rate of infarction in the patient who is

receiving thrombolysis. In the early hours of infarction, beta-blockers act to decrease the work of the heart by lowering heart rate, systemic arterial pressure and contractility, thereby reducing myocardial oxygen demand. The decrease in heart rate caused by beta-receptor blockade, extends the time of diastole and allows greater opportunity for myocardial perfusion. This effect especially increases blood flow to the subendocardium. Overall, these actions lead to the great benefits described above for the AMI patient [1].

In patients who are not receiving thrombolytic therapy, intravenous beta-blockers will not only limit infarct size but will also decrease short-term mortality. These results were evident by the First International Study of Infarct Survival [39]. In this study over 16,000 patients were enrolled within 12 hours of onset of suspected MI symptoms. Patients were immediately given 5-10 mg of intravenous atenolol followed by 100 mg of oral atenolol each day. After 7 days, mortality was reduced from 4.3% to 3.7% ($P<.02$). This corresponds to 6 lives saved per 1000 treated. The decrease in mortality seen in the atenolol patients was apparent from day 1 onward. Similar results were found in the Metoprolol in Acute Myocardial Infarction (MIAMI) trial [40].

Beta-blockers given together with thrombolytic therapy will decrease the chance of ensuing nonfatal reinfarction and recurrent ischemia in AMI patients. Additionally, if given within 2 hours of symptom onset, the beta-blockers can reduce mortality in these patients. These results were shown in the TIMI-II trial [41].

If untoward side-effects such as AV block, extreme bradycardia, or hypotension should occur from beta-blocker therapy, the predicament can be rapidly reversed with administration of a beta-adrenergic agonist such as 1-5 micro grams of isoproterenol [1].

e. Recommendations for Early Therapy [1]:

Class I

1. Patients without a contraindication to beta-adrenoceptor blocker therapy who can be treated within 12 hours of onset of infarction, irrespective of administration of concomitant thrombolytic therapy.
2. Patients with continuing or recurrent ischemic pain.
3. Patients with tachyarrhythmias, such as AF with a rapid ventricular response.

Class IIb
1. Non-Q wave MI
Class III
1. Patients with moderate or severe LV failure or other contraindications to beta-adrenoceptor blocker therapy.

f. Contraindications

The AHA/ACC lists the following relative contraindications to beta-blocker therapy [1]:

heart rate less than 60 bpm; systolic arterial pressure less than 100 mm HG; moderate or severe LV failure; signs of peripheral hypoperfusion; PR interval greater than 0.24 second; Second or third degree AV block; severe chronic obstructive pulmonary disease; history of asthma; severe peripheral vascular disease; insulin-dependent diabetes mellitus.

g. Summary

In summary, all patients with evolving AMI and without contraindications, whether they receive thrombolytic therapy or not, should receive intravenous beta-blockers as soon as possible followed by oral therapy. This therapy has been shown to reduce morbidity and mortality in these patients [1].

6. Angiotensin Converting Enzyme Inhibitors

a. General considerations

ACE inhibitors block the enzyme peptidyl dipeptidase that hydrolyzes angiotensin I to form the potent vasoconstrictor, angiotensin II. They also decrease the rate of bradykinin inactivation by inhibiting the plasma kininase that inactivates bradykinin, a potent vasodilator. Vasodilation occurs as a result of the combined effects of less vasoconstriction due to lower levels of angiotensin II and the potent vasodilating effect of increased bradykinin. Since these agents lower the levels of circulating angiotensin II, ACE inhibitors also reduce aldosterone secretion, leading to decreased sodium and water retention.

b. Coronary Effects

ACE inhibitors reduce vascular resistance, venous tone, and blood pressure causing an increase in cardiac output. These agents also hamper the usual angiotensin II-mediated rise in epinephrine and aldosterone that occurs in CHF. ACE inhibitors also add to the beneficial effects seen in patients who are also receiving a diuretic and/or digoxin. Both morbidity and mortality have substantially decreased from the application of ACE inhibitors among patients with CHF. Therapy with ACE inhibitors has also lessened arrhythmic death, myocardial infarction and strokes [13] .

c. Adverse effects

In patients who are hypovolemic, severe hypertension can occur with the first doses of ACE inhibitors. Other adverse effects include acute renal failure, especially in patients with bilateral renal artery stenosis (or stenosis of the renal artery of a solitary kidney), hyperkalemia, angioedema, and a persistent dry cough, sometimes accompanied by wheezing. ACE inhibitors should not be used in the second or third trimesters of pregnancy [32] .

d. Overview of Clinical Trials

A series of trials (ISIS-4 [24] , GISSI-3 [23] , SMILE [42] , SAVE [43] , AIRE [44] , TRACE) have shown that ACE inhibitor treatment can increase both short- and long-term survival in AMI patients. The patients that benefit most and the only ones that should maintain chronic ACE inhibitor therapy are those patients with low ejection fractions, large infarctions, or clinical evidence of heart failure [5] .

Although all trials in which early oral ACE inhibitors are used in post-infarct patients display a gain from treatment, preliminary data from the ISIS-4 and GISSI-3 trials suggest that ACE inhibitors have greater benefit in patients with anterior infarct or high risk patients with previous infarction, heart failure, and tachycardia. From these studies it is recommended that ACE inhibitor treatment be started in the first 24 hours, preferably after

thrombolysis and once the blood pressure is stable. After 4-6 weeks, if there are no complications and no evidence of LV dysfunction, treatment can be terminated.

Treatment with ACE inhibitors is not advised if systolic blood pressure is less than 100, if there is renal failure or a history of bilateral renal artery stenosis, or if the patient is allergic to ACE inhibitors. Therapy should begin with low oral doses and escalate slowly to a complete dose in 24-48 hours. Intravenous enalaprilat should not be administered [1].

e. Recommendations [1]:

Class I

1. Patients within the first 24 hours of a suspected acute MI with ST-segment elevation in two or more anterior precordial leads or with clinical heart failure in the absence of significant hypotension or known contraindications to use of ACE inhibitors.
2. Patients with MI and LV ejection fraction less than 40% or patients with clinical heart failure on the basis of systolic pump dysfunction during and after convalescence from acute MI.

Class IIa

1. All other patients within the first 24 hours of a suspected or established acute MI, provided significant hypotension or other clear-cut contraindications are absent.
2. Asymptomatic patients with mildly impaired LV function (ejection fraction 40% to 50%) and a history of old MI.

Class IIb

1. Patients who have recently recovered from MI but have normal or mildly abnormal global LV function.

f. Summary

In summary, an oral ACE inhibitor should be administered within hours of hospitalization in the patient with evolving MI with ST segment elevation or LBBB, supposing the patient does not have hypotension and no other contraindications exist. Following initial treatment, the patient with LV systolic dysfunction (ejection fraction below 40%) or clinical CHF should continue treatment indefinitely. However, ACE inhibitors can be terminated by 6 weeks in patients without impaired LV systolic function and without complications [1].

7. Calcium Channel Blockers

a. General Considerations

The calcium channel blockers are divided into three chemical classes, each with different pharmacokinetics and clinical indications. Nifedipine is the prototype of the dihydropyridine family, verapamil represents the diphenylalkylamines and diltiazem is a benzothiazepine. One can understand the role of these drugs by identifying the crucial role that intracellular calcium plays in sustaining smooth-muscle tone and in contracting the myocardium. Calcium reaches muscle cells through specific voltage-sensitive calcium channels. Influx triggers release of calcium from the sarcoplasmic reticulum and mitochondria, further augmenting the cytosolic calcium concentration. Calcium channel antagonists attach to L-type calcium channels in the heart and in smooth-muscle of the coronary and peripheral vasculature, preventing the influx of calcium. This results in vascular smooth muscle relaxation, primarily dilating arterioles [13].

b. Coronary Effects

Cardiac muscle relies highly on calcium influx for normal function. The "slow-response" or calcium-dependent action potentials--causing impulse generation in the sinoatrial node and conduction in the atrioventricular node-- may be limited or blocked by all of the calcium channel blockers. In a dose-dependent fashion, these drugs also decrease cardiac contractility and cardiac output, as excitation-contraction coupling in all cardiac cells is also dependent on calcium flow. Reducing this mechanical function is one of several ways that calcium channel blockers decrease myocardial oxygen demand.

It has been found experimentally that ischemia causes membrane depolarization and subsequent calcium influx. Elevated intracellular calcium in these ischemic cells activates several ATP-consuming enzymes, further depleting the already minimal cellular energy stores and further increasing myocardial susceptibility to ischemic damage. In experimental animals, the calcium channel blockers have been shown to protect against the detrimental

affects of calcium influx by lowering the chance of arrhythmias and decreasing the final size of evolving infarctions [32] .

c. Adverse Effects

The harmful effects of calcium channel blockers are rare and include direct extension of their therapeutic actions. If calcium influx is inhibited to an extreme, severe cardiac depression, including cardiac arrest, atrioventricular block, bradycardia, and congestive heart failure can ensue. Concomitant use of beta-blockers causes increases sensitivity to the cardiodepressant effect of calcium channel blockers. Although infrequent, minor side effects include constipation in 10% of patients, nausea, dizziness, flushing, edema, gingival hyperplasia, headache, and a feeling of fatigue caused by a decrease in blood pressure [13, 32] .

d. Specific agents and overview of clinical trials

1. Nifedipine

Numerous clinical trials, including The Nifedipine Angina Myocardial Infarction Study (NAMIS) [45] , the Norwegian Nifedipine Multicenter Trial [46] , the Trial of Early Nifedipine Treatment in Acute Myocardial Infarction (TRENT) [47] , and the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) [48, 49] ,have been performed with first-generation, nonsustained-release nifedipine to assess the benefit of this calcium channel blocker among patients with AMI. Results from these studies indicate that Nifedipine does not reduce the incidence of reinfarction or mortality whether it is given to patients within 24 hours of acute MI or later. This rule applies to patients regardless of gender, risk level and type of MI, and irrespective of simultaneous use of beta-blockers or thrombolysis. In fact, this form of nifedipine can be harmful in patients with tachycardia or hypotension as it can decrease the necessary perfusion pressure to the heart, cause the arteries adjacent to the infarct-area to dilate disproportionately (thus "stealing" blood from the infarct area), and can cause a reflex sympathetic activation increasing the oxygen demand of the heart.

2. Verapamil

The results found from studies with immediate-release verapamil differ somewhat from the nifedipine trials. While no overall decrease in mortality was found when verapamil was administered to patients post AMI, a reduction in the combined outcome of reinfarction or death was seen when this drug was administered several days after AMI in patients who were not suitable to receive B-adrenoceptor blocking agents. This subgroup of patients must also have intact LV function without clinical evidence of heart failure. If however, the patient has heart failure of bradyarrhythmias within the first 1-2 days after AMI, verapamil administration could be damaging [1]. In one study which randomized 1700 patients under the age of 75 there was a 16.7% reduction in 18 month death or MI when verapamil was administered within 2 weeks of MI [50].

3. Diltiazem

The analysis of two studies, the Muticenter Diltiazem Postinfarction Trial (MDPIT) [51] and the Diltiazem Reinfarction Study (DRS) [52-55] indicates that immediate-release diltiazem (begun 3-15 days after MI in the former study and 24-72 hours after MI in the latter study) will benefit patients who have intact LV function and no heart failure if taken following a Q- wave or non Q- wave infarction. However, in patients with LV dysfunction, diltiazem, like the other calcium channel blockers, is harmful. It is difficult to assess how beneficial diltiazem would be in the treatment of AMI today, as both MDPIT and DRS were conducted in an era prior to the popularity of aspirin use for coronary ischemia. Additionally, the results of MDPIT may be confounded by the use of b-blockers in 53% of the placebo and 55% diltiazem-treated patients [1].

e. Recommendations [1]:

Class I

none.

Class IIa

1. Verapamil or diltiazem may be given to patients in whom B-adrenoceptor blockers are ineffective or contraindicated (i.e., bronchospastic disease) for relief of ongoing ischemia or control of a rapid

ventricular response with AF after acute MI in the absence of CHF, LV dysfunction, or AV block.
Class II b
1. In non-ST-elevation infarction, diltiazem may be given to patients without LV dysfunction, pulmonary congestion, or CHF. It may be added to standard therapy after the first 24 hours and continued for 1 year.
Class III
1. Nifedipine (short acting) is generally contraindicated in routine treatment of acute MI because of its negative inotropic effects and the reflex sympathetic activation, tachycardia, and hypotension associated with its use.
2. Diltiazem and verapamil are contraindicated in patents with acute MI and associated LV dysfunction or CHF.

f. Summary

There are no studies that support the use of calcium channel blockers in early therapy or secondary prevention for the vast majority of typical AMI patients. In fact, in certain patient populations with cardiovascular disease they seem to be harmful, as they can exacerbate ischemia and cause death from myocardial depression or reflex tachycardia. Diltiazem and verapamil may lower the chance of reinfarction in patients without ST-segment elevation or LBBB in whom pulmonary congestion is absent. However, it is not certain whether these drugs are advantageous beyond aspirin and beta-blocker therapy. Immediate-release, first-generation dihydropyridines such as nifedipine are contraindicated in the acute MI patient. There are no data to assess the utility of second-generation dihydropyridines in AMI management [1]. Hence, calcium channel blockers should be reserved as second- or third- line agents after nitrates and beta-blockers for treatment of hypertension or ischemia [5].

8. Inotropic Agents

a. General Considerations

Positive inotropic agents strengthen cardiac muscle contractility, and thus expand cardiac output. Despite their distinct mechanisms, each inotropic agent will elevate cytoplasmic calcium concentration and thereby intensify the contractility of cardiac muscle [13].

Three classes of inotropic agents can be described: those with predominant vasoconstrictive activities; catecholamines that mostly affect inotropy and have very little vasoconstrictive properties; and phosphodiesterase inhibitors which mainly have vasodilating properties.

Dopamine and norepinephrine are the prototypes of the vasoconstrictor inotropic agents. Norepinephrine is essentially a vasoconstricting agent with positive inotropic effects. The exact actions of dopamine depend on dosage. At low doses it acts mainly on dopamine receptors to dilate the renal vasculature and on beta- adrenergic receptors to moderately increase contractility. If doses are increased, the beta-1 receptor activation dominates leading to positive chronotropic and inotropic effects. At still higher doses, dopamine leads to vasoconstriction as the alpha effects predominate.

Dobutamine is the prototypical inotropic agent that is a catecholamine without vasoconstriction properties. It exerts positive inotropic effects by stimulating beta-1 receptors. Amrinone and milrinone are phosphodiesterase inhibitors developed with the hope that they would improve cardiac output without predisposing to arrhythmias, as do the catecholamines. These agents both increase contractility and vasodilation, with a greater effect on preload than catecholamines. Long-term amrinone use has been associated with toxicity and long-term milrinone use with excessive mortality, and thus the use of these agents has not been as promising as was anticipated [1].

b. Digitalis

1. General Considerations

Since most of the cardiac glycosides are derived from the digitalis (foxglove) plant they are often referred to as digitalis or digitalis glycosides. Chemically alike, these compounds can all strengthen the contractility of the heart muscle, a "positive" inotropic action, and are therefore popular in treating heart failure. Like the antiarrhythmic drugs, the cardiac glycosides affect the flows of sodium and calcium ions in the cardiac muscle. These drugs have a low therapeutic index--they display only a small gap between a dose

that is therapeutically effective and one that is toxic or even lethal. The most popular agent among the digitalis glycosides is digoxin.

2. Mode of Action

The two main actions of digitalis responsible for its therapeutic effects include its regulation of cytosolic calcium concentration and increased contractility of the cardiac muscle. Cardiac glycosides inhibit the action of the sodium-potassium ATPase pump of the cardiac cell membrane. They reversibly bind to the pump causing an increase in the intracellular sodium concentration, favoring the transport of calcium into the cell via the sodium-calcium exchange mechanism. The increased levels of intracellular calcium increase the systolic force of contraction.

The increased systolic force of contraction caused by digitalis glycosides is followed by several additional changes in cardiac physiology. Increased inotropy allows the cardiac output of the failing heart to more closely resemble that of the normal heart. This, in turn, results in a decrease in end-diastolic volume and an increased ejection fraction. This improvement in contraction efficiency results in improved circulation and a decrease in sympathetic activity. A decrease in peripheral resistance and slower heart rate follow. In addition, vagal tone is increased contributing to the decrease in heart rate. Overall, myocardial oxygen demand is lowered [13].

The electrical effects of digoxin on cardiac muscle lead to an early, short prolongation of the action potential, followed by a late period of shortening, especially of the plateau phase. This decrease in action potential duration is probably due to an influx of potassium caused by an increased amount of intracellular calcium. As a result of the shortened action potential, atrial and ventricular refractory periods are shortened as well.

3. Adverse Effects

"Digitalis toxicity" is one of the most frequently occurring adverse drug reactions. When the concentration of digitalis reaches toxic levels, the resting membrane potential becomes even more negative as a result of inhibition of the usual actions of the sodium-

potassium-ATPase pump. As toxicity continues, normal action potentials are followed by oscillatory depolarizing afterpotentials called "delayed afterdepolarizations." These afterpotentials result from overloading the intracellular calcium stores and oscillations in the intracellular concentration of free calcium ion. These afterpotentials interfere with normal conduction in several ways. When below threshold, they cause the resting membrane potential to further decrease. If the afterpotential reaches threshold it will produce an action potential which forms a premature ventricular depolarization. Bigeminy will result on the EKG if the purkinje system regularly experiences these premature depolarizations. As toxicity progresses, these premature action potentials can elicit suprathreshold afterpotentials of their own. The result is a self-sustaining arrhythmia--ventricular tachycardia. With progression, this arrhythmia may give way to ventricular fibrillation [5].

Other adverse effects of digitalis include gastrointestinal effects such as anorexia, nausea, and vomiting. CNS disturbances such as headache, fatigue, and confusion may also occur. Visual disturbances include obscure vision, modification of color perception, and haloes of dark objects [13].

4. Overview of Clinical Trials

Although the inotropic properties of digitalis were described as far back as 1785, its place in AMI management is still controversial. Reexamination of certain previous observational studies on digitalis reveal an association between its use and an increase in mortality. Other studies, however, show no effect on mortality. Recently it has been revealed that digitalis improves symptoms and positively affects the neurohormonal system in patients with LV systolic dysfunction [1]. The Digitalis Investigator Group (DIG) [56] compared digitalis to placebo with regard to all-cause mortality among 7788 CHF patients without rhythm disturbances. CHF was caused by ischemic disease in 70% of the study patients, and greater than 90% of the patients were also treated with ACE inhibitors and/or diuretics. Overall, the study revealed that digoxin did not reduce total mortality. Digoxin-treated patients, however, did have less deaths due to CHF and less combined

hospitalizations and deaths due to heart failure. There was a suggestion, however, of increased deaths from supposed arrhythmia or MI in the digoxin group.

The current recommendation for Digoxin use, based on clinical experience, advises the administration of digoxin to certain post-MI patients who have supraventricular arrhythmias or CHF that is not responsive to ACE inhibitors or diuretics [1].

9. Diuretics

The patient hospitalized for AMI should be treated with diuretics if he/she suffers from heart failure. Usually, intravenous furosemide is administered. The patient with heart failure should be administered an afterload reducing agent as well [1].

10. Hypolipidemic Agents

Recent trials have shown that substantially lowering cholesterol levels in patients at high risk for coronary heart disease or patients with established, but stable coronary heart disease, with the use of 3-hydroxy-3-methylglutaryl-coenzyme A reduces cardiovascular morbidity and mortality [57-59]. Hence, it is well established that the long term management of the patient status post-AMI should involve lipid reduction. ACC/AHA guidelines for long term management of the patient after AMI state that in addition to receiving aspirin, a beta-blocker, and a selected dose of an ACE inhibitor after AMI, the patient should be instructed about weight control and educated about a diet low in saturated fat and cholesterol. If, despite dieting, the patient maintains a low-density lipoprotein (LDL) cholesterol measurement greater than 130 mg/dL, drug therapy with the goal of reducing LDL to less than 100 mg/dL should be initiated. Additionally, smoking cessation is essential, and an ultimate goal of exercising for 20 minutes, three times a week, at the level of brisk walking, should also be met [1].

However, it is still uncertain whether lipid-lowering drugs should be administered immediately after AMI, in doses that would acutely lower lipid levels. Such reduction might stabilize coronary plaques and lessen early, recurrent ischemic events. The MIRACL study, currently underway, has been designed to address this issue [60].

II. Statement of Purpose and Hypothesis

We hypothesized that the availability of resources influences the type of care administered to patients with AMI. Hence, we evaluated and compared the procedural and pharmacologic management of patients in hospitals of different sophistication levels. Additionally, we hypothesized that application of clinical guidelines in practice is imperfect and that pharmacologic treatment does not always conform to the recommendations of these published guidelines. Thus, we assessed for trends in pharmacologic treatment over time to see if practice patterns reflect the results of published clinical trials.

III. Methods

A. Experimental Design

To evaluate our hypothesis, we analyzed data from the CHAMP study, a prospective post-MI study in the VA sector which evaluated warfarin and aspirin in combination against aspirin. We determined utilization rates of (1) cardiac procedures including PTCA and CABG and (2) pharmacotherapies including ACE inhibitors, antiarrhythmics, beta-blockers, calcium channel blockers, digitalis, diuretics, nitrates, and hypolipidemic agents in patients with proven myocardial infarction (transmural or non-transmural) who participated in the CHAMP study. Utilization rates are computed per calendar year, according to level of hospital sophistication, and analyzed over the course of the study (1993-1997). Ensuing trends are plotted. A determination is made as to whether the resources available at the respective hospitals influenced patient care, whether these practice patterns changed over time, and whether trends in clinical practice reflect the results of concurrent clinical trials.

B. Data Source: The CHAMP Study

The CHAMP study, designed by Michael Ezekowitz, M.D., Ph.D. and Louis Fiore, M.D. provides a unique opportunity to test our hypotheses. Designed to demonstrate whether the combination of oral anticoagulation and antiplatelet therapy (i.e., warfarin and aspirin) is superior to aspirin alone in reducing overall mortality following acute myocardial infarction, this study was a two-arm, prospective, randomized, unblinded trial. Approximately 5000 patients admitted to the participating VA hospitals between 1992 to 1998 with proven myocardial infarction[8] were randomized to receive either warfarin and aspirin in combination or aspirin alone.

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[8] For the CHAMP study, the diagnosis of AMI is defined as the presence of two of the following : chest pain discomfort typical of AMI, EKG changes typical of AMI and blood enzyme changes typical of AMI (at least one of the following: MB isoenzyme of creatine kinase in excess of 4 % of the total creatine kinase level, elevated total lactic dehydrogenase with an abnormal reversal of the ratios of LDH 1 to LDH 2 or the

All hospitalized patients with a diagnosis of AMI within the previous 14 days were screened for admission to the study. Patients were considered ineligible for enrollment based on specific exclusion criteria that are listed in Table A.

None of the following conditions were reasons for exclusion: history of coronary artery bypass surgery, coronary artery angioplasty either before or after the index AMI and use of thrombolytic therapy for any AMI. Additionally, there was no age cutoff in this study.

All eligible patients were asked to participate in the study and if the patient and his physician agreed to randomization, an "Informed Consent Form" and "Baseline Data Form" were completed. Hence, baseline data were obtained on all eligible consenting patients within 14 days of the index AMI and prior to hospital discharge. The information included most of the known predictors for long-term survival following AMI. The baseline form recorded information about subjects' demographics, smoking, and medical history. Additional information included the extent, location and complications (if any) of the index infarction; ejection fraction; serum chemistries; medical therapy; and invasive procedures. Not included were predictors that were not routinely available on all patients such as a post AMI exercise tolerance test or results of cardiac catheterization.

Once consent and baseline data were obtained, the local study coordinator would contact the coordination center and the patient would be randomized. At this time the patient's "Randomization Form" would be completed.

The assigned therapy was initiated immediately. All patients were contacted every three months and seen every six months to complete the "Follow-up Visit Form." The follow-up form recorded information about study withdrawal and compliance to assigned therapy. Additionally, it included information on any intercurrent events as well as procedures/conditions since the last visit.

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elevation of two or more of lactic dehydrogenase, creatine kinase or aspartate transaminase to twice the upper limit of normal without an obvious other cause for the rise).

C. Data Acquisition Specifically Related to This Project

Baseline data (collected within two weeks from index AMI) as well as three-month follow-up data were available for our investigation for the six years of the CHAMP study (1993-1998). Information collected at these times concerning the cardiac procedures and pharmacologic treatment for the index AMI served as the basis for our analysis. Table B lists the categories of the information which were collected from the CHAMP database and analyzed based on the year that the patient was enrolled into the study and based on what hospital type the patient was initially treated at.

Seventy-five VA hospitals throughout the U.S., including both large university-associated VA medical centers as well as smaller hospitals, participated in the study. Hence, participating hospitals differed in their available resources and capabilities. In preparation for our analysis, these hospitals were contacted by telephone to determine their capabilities for cardiac care. Hospitals were grouped into three classes according to level of resources available: Group 1 hospitals did not have a cardiac catheterization laboratory and did not perform cardiovascular surgery; Group 2 hospitals performed cardiac catheterization procedures, but did not perform cardiac surgery or angioplasty on site; Group 3 hospitals provided both cardiac catheterization procedures and cardiac surgery on site. This Categorization of participating hospitals fashion enabled us to analyze data by level of hospital sophistication. This classification system is depicted in Table C.

D. Statistical Methods

Trends in procedure use were examined at the time of randomization and at three months post randomization, by year of enrollment (1992-1997), and by hospital sophistication. Medication use was analyzed by year of enrollment and by hospital sophistication. Chi-square analyses were used to test for crude differences in procedure and pharmacologic utilization across hospital categories and across years of enrollment. A Mantel-Haenszel Extension Test for linear trend was used to examine trends in procedure utilization and medication use across years of study enrollment. For the analysis of

medication/procedure use by hospital type, percentages of the total population randomized to each hospital type are reported for each medication or procedure use. For the analysis of management by year of enrollment, percentages of the total enrolled trial population were reported for each category of medication or procedure used for each year.

IV. Results

A. Champ Enrollment by Hospital Cardiac Capability (Fig 1)

Participating hospitals were divided into three groups. Group 1, which contained 22.4% of patients recruited in the CHAMP study, had no cardiac catheterization laboratory. Group 2, which comprised 22.6% of patients recruited, had a cardiac catheterization laboratory but did not have the capability to perform cardiac surgery. Group 3, the most advanced hospital grouping, encompassed 54.9% of the recruited patients and had the capability for diagnostic catheterization as well as both catheter based and surgical revascularization.

B. Champ Enrollment 1993-1998 (Fig 2)

The percent of patients enrolled in the CHAMP study was computed for each study year. In 1993, 700 patients (14.8% of the patients) were randomized into the study. Enrollment increased in 1994 to 1115 patients (23.5% of the total) and further increased to 1125 patients in 1995 (23.9%). For the last three years of the study, however, enrollment dropped to 847 patients in 1996 (17.9%), 817 patients in 1997 (17.3%) and to the lowest enrollment of 129 patients (2.7% of total) in 1998. For the analysis of procedure and medication use over time, we excluded data from 1998 because of the small number of patients recruited in this year. Patient data from 1998, however, are included in the analysis of management by hospital type, as in this analysis all patients recruited over the 1993-1998 time period are considered together.

C. CHAMP Trends in Procedure Use

1. CHAMP CABG Rates

a. Total CABG (Within 90 days) Post-MI by Year (Fig 3)

The trend in CABG use over time increased in a statistically significant manner over time: 16.6%, 19.0%, and 21.4% in 1993, 1995, and 1997, respectively (p(trend) =0.001).

b. CABG Rates by Hospital Type

1. Early (Within 14 Days) vs. Later (Between 14-90 Days) CABG Post-MI by Hospital Type (Fig 4)

CABG procedure rates were stratified according to the categories of "early CABG" -- CABG within 14 days of index infarct--and "later CABG"--CABG between 15-90 days following index infarct. There is a significant difference in the percent of patients undergoing both early and later CABG when rates are analyzed by hospital type. Unsophisticated hospitals (group 1) have the lowest rate of early CABG but highest rate of later CABG. Sophisticated hospitals (group 3), however, have the highest rate of early CABG and a lower rate of later CABG. Yet, when all CABG procedures performed within 90 days of index MI are considered together, unsophisticated and sophisticated hospitals have comparable rates.

Only 1.8% of the patients treated in Group 1 hospitals underwent early CABG. The percent is higher (3.3%) for patients admitted to Group 2 hospitals, and highest (7.7%) among patients treated at Group 3 hospitals (p=0.001). However, the results are very different for later CABG (CABG between 14-90 days). Later CABG rates were highest in patients initially admitted to group 1 hospitals (19.2%). Rates of later CABG were significantly lower in Group 2 (13.0%) and group 3 (14.6%) (p=0.001).

2. Total CABG (Within 90 Days) Post-MI by Hospital Type (Fig 4)

When both early and later CABG rates are considered together, group 1 (19.3%) and group 3 hospitals(20.9%) have comparable rates, whereas group 2 hospitals (15.0%) have a rate that is significantly lower (p=0.001).

c. CABG Rates by Hospital Type by Year

1. Early CABG (Within 14 Days Post-MI) by Hospital Type by Year (Fig 5)

In group 3 hospitals, the rates of cardiac surgery increased significantly over time, ranging from 4.1% in 1993 to 6.4% in 1995 to 11.4% in 1997 (p(trend)=0.001). Group 1

and group 2 hospitals varied by year. In 1993 early CABG rates were 2.6% and 3.7% for hospital groups 1 and 2, respectively. In 1995, the group 1 rate decreased (0.8%), and the rate in group 2 increased (4.6%). In 1997, CABG rates increased in group 1 hospitals (1.9%) but decreased in group 2 (1.0%).

2. Later CABG (Between 14-90 Days) Post-MI by Hospital Type by Year (Fig 6)

In contrast to the rates of early CABG that increased over time in sophisticated hospitals, the rates of later CABG increased dramatically over time in unsophisticated hospitals. Later CABG rates in group 1 hospitals ranged from 12.9% to 19.3% to 27.5% in 1993, 1995, and 1997, respectively (p(trend)=0.001). In the other hospital groups rates were relatively unchanged (11.2% to 12.6% to 13.5% in 1993, 1995, and 1997, respectively for group 2 hospitals, (p(trend)=0.517) and 16.1% to 15.1% to 13.5% in 1993, 1995, and 1997, respectively for group 3 hospitals (p(trend)=0.571).

3. Total CABG (Within 90 Days) Post-MI by Hospital Type by Year (Fig 7)

Overall, there was a significant increase in total CABG over time in group 1 hospitals, whereas total CABG in group 2 and group 3 hospitals remained remarkably constant over time. Group 1 hospitals increased their rates of total CABG over time by 102%, from 14.0% to 18.8% to 28.3% in 1993, 1995 and 1997, respectively (p (trend)=0.001). In group 2 hospitals, no significant trend is seen for total CABG rate; total CABG rates over time ranged from 13.9% to 15.6% to 13.7% in 1993, 1995, and 1997, respectively (p(trend)=0.686). In group 3 hospitals, total CABG rates over time increased by 18.0% and ranged from 19.1% to 20.4% to 22.6% in 1993, 1995, and 1997, respectively (p(trend)=0.108).

2. CHAMP PTCA Rates

a. Total PTCA (Within 90 days) Post-MI by Year (Fig 8)

Overall, PTCA use increased significantly from 1993 to 1997, with 15.4% of patients undergoing PTCA in 1993, 21.6% in 1995 and 29.3% in 1997 (p(trend)=0.036).

b. PTCA Rates by Hospital Type

1. Early (Within 14 days) vs. Later (Between 14 – 90 Days) PTCA Post-MI by Hospital Type (Fig 9)

PTCA procedure rates, like those of CABG, were stratified into two classes: early PTCA -- PTCA within 14 days of index infarct --and later PTCA--PTCA between 15-90 days following index infarct.

Early PTCA rates increased significantly with increasing hospital sophistication level, as demonstrated by rates of 5.0%, 8.6%, and 23.5% for groups 1, 2, and 3, respectively (p=0.001). Later PTCA remained constant among the three hospital types, however, with rates of 9.6%, 9.3%, and 8.8% for groups 1, 2, and 3, respectively (p=0.75).

2. Total PTCA (Within 90 days) Post-MI by Hospital Type (Fig. 9)

Overall, however, when both early and later PTCA utilization rates are considered together, there is a significant increase with increasing hospital sophistication. Group 3 hospitals had the greatest utilization rates (29.5%), group 2 in the middle (16.5%) and group 1 the least (13.4%) (p=0.001).

c. PTCA Rates by Hospital Type by Year

1. Early PTCA (Within 14 Days) Post-MI by Hospital Type by Year (Fig 10)

Early PTCA rates increased significantly over time in group 3 hospitals, ranging from 15.9% to 22.5% to 29.8% in 1993, 1995, and 1997, respectively (p (trend)=0.001). In group 2 hospitals a significant upward trend is seen in early PTCA rates as well, with

rates ranging from 3.7% to 6.7% to 12.3% in 1993, 1995, and 1997, respectively (p(trend)=0.006). In group 1 hospital types, however, rates of early PTCA did not change significantly over time, with rates ranging from 5.2% to 2.9% to 3.8% in 1993, 1995 and 1997, respectively (p(trend)=0.366).

2. Later PTCA (Between 14 – 90 Days) Post-MI by Hospital Type by Year (Fig 11)

Rates of later PTCA increased significantly over time in group 1 hospitals, ranging from 3.4% to 6.3% to 15.0% in 1993, 1995, and 1997, respectively (p(trend)=0.004). There was no significant linear trend, however, in group 2 or group 3 hospitals. Group 2 hospitals had utilization rates of 7.2%, 6.9%, 10.8%, 9.8% and 11.3% in years 1993-1997, respectively (p(trend)=0.102). Group 3 hospitals had utilization rates of 8.2%, 9.6%, and 7.7% in 1993, 1995, 1997, respectively (p(trend)=0.924).

3. Total PTCA (Within 90 Days) Post-MI by Hospital Type by Year (Fig 12)

All three hospital types show significant increases in total PTCA rates over time. Total PTCA rates in group 1 hospitals were 8.3%, 15.9%, 8.3%,15.0%, and 18.2% from 1993-1997, respectively (p(trend)=0.036). Total PTCA rates in group 2 hospitals are 9.7%, 14.9%, 16.0%, 17.2%, 22.8% from 1993-1997, respectively (p(trend)=0.001). Total PTCA rates in group 3 hospitals were 22.1%, 26.5%, 28.7%, 31.6%, and 36.2% from 1993-1997, respectively (p(trend)=0.001).

D. CHAMP Trends in Medication Use

1. Thrombolytics

a. Thrombolytic Use by Year (Fig 13)

Thrombolytic use was relatively stable from 1995 to 1997. Use increased from 1993 (29.6%) to 1994 (36.0%) and then decreased again in 1995 (28.7%). Usage increased slightly in 1996 (29.7%) and decreased in 1997 (29.6%), (p (trend = 0.071).

b. Thrombolytic Use by Hospital Type (Fig 14)

There is a significant decrease in thrombolytic use with increasing hospital sophistication level. Group 1 hospitals had the greatest thrombolytic usage (33.5%), group 2 hospitals had a lower usage (32.4%) and group 3 had the lowest thrombolytic usage (29.3%) (p=0.026).

c. Thrombolytic Use by Hospital Type by Year (Fig 15)

Overall, thrombolytic utilization trended downward in group 1 hospitals (p(trend)=0.006), but trended upward among group 2 hospitals (p(trend)=0.001). For group 3 hospitals, utilization also trended downward (p(trend) = 0.005).

2. ACE Inhibitors

a. ACE Inhibitor Use by Year (Fig 16)

Our data show a significant increase in ACE inhibitor use from 1993 to 1997. In 1993, 26.4% of study patients were treated with ACE inhibitors, and increased to 31.0% in 1995, and 43.4% in 1997 (p (trend)= 0.001).

b. ACE Inhibitor Use by Hospital Type (Fig 17)

There was no significant difference in ACE Inhibitor use by hospital type. Group 3 hospitals had the highest use of ACE inhibitors (33.3%), with group 1 (32.8%) and Group 2 (31.3%) hospitals having the lowest utilization rates (p=0.503).

c. ACE Inhibitor Use By Hospital Type By Year (Fig 18)

Analysis of ACE inhibitor use according to hospital type and year reveals that there was a significant increase in ACE inhibitor use across years for all hospital types. Group 1 utilization rates increased over time: 27.5%, 30.8%, and 44.0% for 1993, 1995, and 1997, respectively (p(trend)=0.029). Group 2 utilization rates increased over time: 25.5%, 28.2%, and 46.7% for 1993, 1995, and 1997, respectively (p(trend)=0.001). Group 3 utilization rates increased as well: 26.2%, 31.8%, and 41.6% for 1993, 1995, and 1997, respectively (p(trend)=0.001).

3. Beta-Blockers

a. Beta-Blocker Use by Year (Fig. 19)

Beta-Blocker use significantly increased from 1993 to 1997. In 1993, 63.4% of patients were treated with beta-blockers. This number increased to 71.1% in 1995 and to 79.2% in 1997 (p(trend)= 0.001).

b. Beta-Blocker Use by Hospital Type (Fig 20)

There is a significant difference in beta-blocker use according to hospital type. Use is highest in group 2 hospitals (74.7%) and lowest in group 1 hospitals (63.6%), with an in-between rate (73.2%) in group 3 hospitals (p=0.001).

c. Beta-Blocker Use by Hospital Type by Year (Fig 21)

Analysis of beta-blocker use according to hospital type and year reveals that there was a significant increase in beta-blocker use over time for all hospital types. Group 1 utilization rates increased from: 51.3% to 63.6% to 74.8% for 1993, 1995, and 1997, respectively (p(trend)=0.001). Group 2 utilization rates increased as well: 70.3%, 74.0%, and 83.4% for 1993, 1995, and 1997, respectively (p(trend)=0.001). So too, group 3 utilization rates increased over time: 67.1%, 72.5%, and 78.8% for 1993, 1995, and 1997, respectively (p(trend)=0.001).

4. Calcium Channel Blockers

a. Calcium Channel Blocker Use by year (Fig 22)

Data show a significant decrease in calcium channel blocker use between 1993-1997. Use is highest in 1993 (32.3%), but decreased in 1995 (25.4%), and in 1997 (17.8%) (p(trend)= 0.001).

b. Calcium Channel Blocker Use by Hospital Type (Fig 23)

No differences were found for calcium channel blocker use by hospital type:, 25%, 22.9%, and 26.1% for groups 1, 2 , and 3, respectively (p=0.127).

c. Calcium Channel Blocker Use by Hospital Type by Year (Fig 24)

Analysis of calcium channel blocker use according to hospital type and year reveals that there was a significant decrease in calcium channel blocker use across years for all hospital types. Group 1 utilization rates decreased over time: 34.7%, 23.4%, and 19.5% for 1993, 1995, and 1997, respectively (p(trend)=0.001). Group 2 utilization rates decreased over time as well: 27.9%, 22.7%, and 17.1% for 1993, 1995, and 1997, respectively (p(trend)=0.001). Group 3 utilization rates also decreased over time: 33.2%, 27.3%, and 17.5% for 1993, 1995, and 1997, respectively (p(trend)=0.001).

5. Digitalis

a. Digitalis Use by Year (Fig 25)

Data are suggestive for a decreasing trend in digitalis use from 1993 to 1998. In 1993, digitalis use was at its highest , 8.7%, decreasing to 7.5% in 1995 and 6.7% in 1997, (p(trend)= 0.124).

b. Digitalis Use by Hospital Type (Fig 26)

Data show a significant difference in digitalis use according to hospital type. Digitalis was greatest in group 3 (8.4%), compared with group 2 (8.0%) and group 1 (5.1%) hospitals (p= 0.001).

c. Digitalis Use by Hospital Type by Year (Fig 27)

Analysis of digitalis use according to hospital type and year reveals that there was a significant decrease in digitalis use across years in group 3 hospitals only. Group 1 utilization rates decreased over time: 5.7%, 5.4%, and 4.4% for 1993, 1995, and 1997, respectively (p(trend)=0.077). Group 2 utilization rates wavered over time: 6.1%, 10.1%, and 6.6% for 1993, 1995, and 1997, respectively (p(trend)=0.851). Group 3 utilization rates decreased over time: 11.8%, 6.9%, and 7.6% for 1993, 1995, and 1997, respectively (p(trend)=0.007).

6. Diuretics

a. Diuretic Use by Year (Fig 28)

We found no apparent linear trend in diuretic use over time. Rather, diuretic use shows a wavering pattern over time, with the initial rate in 1993 (17.3%) being lower than the final rate in 1997 (19.4%). The rate decreases from 1993 to 1994 (16.0%), increases by 1995 (17.1%), and then drops in 1996 (13.9%), only to reach its highest level in 1997, (p(trend)= 0.579).

b. Diuretic Use by Hospital Type (Fig 29)

Data show a significant difference in diuretic use according to hospital sophistication. Use was greatest in group 1 (19.9%) lower in group 2 (15.7%) and slightly lower in group 3 (15.6%), (p= 0.004).

c. Diuretic Use by Hospital Type by Year (Fig 30)

Analysis of diuretic use reveals that there was no uniform trend in the use of these agents by years or by hospital type. Group 1 utilization rates fluctuated over time: 11.9%, 24.6%, and 22.6% for 1993, 1995, and 1997, respectively (p(trend)=0.212). Group 2 utilization rates fluctuated over time as well: 23.0%, 16.0%, and 18.0% for 1993, 1995, and 1997, respectively (p(trend)=0.895); while, group 3 utilization rates remained relatively stable over time: 17.4%, 14.0%, and 18.8% for 1993, 1995, and 1997, respectively (p(trend)=0.966).

7. Nitrates

a. Nitrate Use by Year (Fig 31)

Data show a significant decreasing trend in nitrate use over time. Although initially, utilization minimally increases from 1993 (78.5%) to 1994 (78.7%), from 1994 until 1997 there is a significant decline in nitrate use. Use declined to 77.8% in 1995, and 71.6% in 1997, (p(trend)= 0.001).

b. Nitrate Use by Hospital Type (Fig 32)

Data show a significant difference in nitrate use between hospital type 1 (80.3%) and the other hospital types, hospital type 2 (75.1%) and hospital type 3 (75.1%) (p=0.002).

c. Nitrate Use by Hospital Type by Year (Fig 33)

Analysis of nitrate use according to hospital type and year reveals that there was a significant decrease in nitrate use across years for groups 1 and 3, but not for group 2. Group 1 utilization rates decreased over time: 78.2%, 87.1%, and 69.2% for 1993, 1995, and 1997, respectively (p(trend)=0.005). Group 2 utilization rates remained relatively stable: 78.2%, 75.6%, and 71.1% for 1993, 1995, and 1997, respectively (p(trend)=0.109); while group 3 utilization rates decreased over time: 78.8%, 74.9%, and 72.7% for 1993, 1995, and 1997, respectively (p(trend)=0.001).

8. Hypolipidemic Agents

a. Hypolipidemic Agent Use by Year (Fig 34)

Data show a significant increase in the use of lipid lowering medication between 1993-1997. In 1993, utilization rate was 8.7%, increasing to 14.2% in 1995, and 39.2% in 1997, (p(trend)= 0.001).

b. Hypolipidemic Agent Use by Hospital Type (Fig 35)

Data show a significant difference in lipid lowering medication utilization according to hospital type. Use was highest in group 2 (21.3%), slightly lower in group 3 (20.9%) and lowest in group 1 (15.5%), (p= 0.001).

c. Hypolipidemic Agent Use by Hospital Type by Year (Fig 36)

Analysis of hypolipidemic agent use according to hospital type and year reveals that there was a significant increase in hypolipidemic agent use across years for all hospital types. Group 1 utilization rates increased over time: 5.7%, 12.5%, and 35.2% for 1993, 1995, and 1997, respectively (p(trend)=0.001). So too, group 2 utilization rates increased over time: 9.1%, 15.6%, and 40.0% for 1993, 1995, and 1997, respectively

(p(trend)=0.001), and group 3 utilization rates increased as well: 10.3%, 14.4%, and 40.3% for 1993, 1995, and 1997, respectively (p(trend)=0.001).

V. Discussion

A. Cardiac Procedures

Our results showed that over a six year period (1993-1997), cardiac procedures were increasingly employed in the management of VA patients diagnosed with AMI. PTCA and CABG, when considered together, increased by 59% in the time period under investigation (32% in 1993, 51% in 1997). Considered individually, both CABG and PTCA utilization increased over the six year study period; CABG increased by 29% (16.57% in 1993, 21.42% in 1997) (Figure 3), and PTCA increased by 90% (15.43% in 1993, 29.25% in 1997) (Figure 8). This pattern of increased procedure application in the treatment of patients with ischemic heart disease is evident in all hospitals groups in our study (Figure 7, Figure 12) and is consistent with the trend that has been observed in the United States over the last two decades. Statistics collected between 1980 and 1992 revealed a 163% increase in coronary angiography rates and a 102% increase in CABG rates [61].

The question arises as to whether this aggressive approach with regard to cardiac procedures translates into better outcomes for AMI patients. Tu and colleagues [62] address this issue with a comparison of the one-year mortality rate in a cohort of aggressively managed patients from the United States to a less aggressively managed cohort from Ontario, Canada. They found that despite the differences in management, the two cohorts had virtually identical one-year mortality rates. They concluded that, overall, their study favored the more conservative approach to revascularization that is employed in Canada.

However, as pointed out by Krumholz, in determining the overall impact of coronary revascularization, one must consider not only mortality rates, but also the patients' quality of life and functional status, as well as the costs incurred [63]. Hence, analyzing the outcome data for the patient population included in our study would provide

important information for interpreting the potential benefits of our increasingly aggressive management appraoch. This analysis is currently underway but is beyond the scope of this work.

Although hospitals of all sophistication levels have increased their utilization of cardiac procedures overall, our study reveals a significant difference in procedure utilization based on hospital sophistication level. Patients admitted to hospitals of highest sophistication (group 3) with capabilities for both cardiac catheterization and surgery, who were treated with a procedure, were most likely to be treated with "early" PTCA (within 14 days following index MI) rather than "later" PTCA (between 14 - 90 days following index MI), "early" CABG (within 14 days following index MI), or "later" CABG (between 14 – 90 days following index MI). In 1997, 29.82% of patients randomized to group 3 hospitals were treated with early PTCA whereas 7.73% had later PTCA, 11.41% had early CABG and 13.53% had later CABG. Totaling all early PTCAs performed in the six years under investigation, the rate of early PTCA increased significantly with increasing level of hospital sophistication: 5.04% in group 1, 8.55% in group 2, and 23.45% in group 3 (p=0.001) (Figure 9).

Patients admitted to less sophisticated hospitals (groups 1 and 2), however, and treated with a procedure, were most likely to be referred out to more sophisticated hospitals and treated with "later" CABG. In 1997, 27.25% of patients admitted to group 1 hospitals were treated with later CABG, whereas 1.9% had early CABG, 15.03% had later PTCA and 3.77% had early PTCA. Similarly, in 1997, 13.45% of patients admitted to group 2 hospitals were treated with later CABG, whereas 0.95% had earlier CABG, 11.33% had later PTCA and 12.32% had early PTCA. Totaling all later CABG procedures performed in the six years under investigation, the rate of later CABG is highest in group 1 hospitals--19.16% in group 1, 13% in group 2, and 14.64% in group 3 (p=0.001) (Figure 4).

Overall, our results show that patients admitted to the most sophisticated hospitals and treated with a procedure tend to be treated "early," whereas those admitted to

unsophisticated and intermediate hospitals are treated "later." Hospitals of greatest sophistication favor PTCA, whereas less sophisticated hospitals favor CABG. (The latter trend is consistent with recommendations that PTCA should be performed within 60-90 minutes following diagnoses of AMI, and hence, later PTCA would not be advisable).

This evidence of a discrepancy in procedural care based on the resources available supports the findings of Wright et al. who reported that rates of cardiac catheterization (OR 3.07; 95% CI 2.87-3.28), CABG (OR 1.48; 95% CI 1.33-1.65), and PTCA (OR 2.93; 95% CI 2.57-3.34) were significantly higher in patients admitted to sophisticated versus relatively unsophisticated hospitals [64]. Our study shows, however, that although both CABG and angioplasty rates are higher in patients admitted to sophisticated hospitals, when all data are pooled over the six year time period, procedure use increases in unsophisticated hospitals. In 1996 and 1997, unsophisticated hospitals had higher CABG rates than sophisticated hospitals (1996, group 1=25%, group 3=22.72%; 1997, group 1=28.30%, group 3=22.6%) (Figure 7). PTCA rates, however, were higher in more sophisticated hospitals (1996, group 1=15%, group 2 = 31.64%; 1997, group 1=18.24%, group 3 = 36.24%) (Figure 12).

Wright et al. also studied patient outcomes in VA facilities by hospital sophistication level. They concluded that patients admitted to relatively unsophisticated hospitals had significantly higher mortality compared with patients initially admitted to more sophisticated hospitals [64]. Other studies, however, have found no differences in mortality based on the level of hospital sophistication [65-67]. The question of whether variation in hospital sophistication level affects patient outcome is most significant for the VA health care system, as our study showed that a substantial minimum of VA patients (in the CHAMP study 22%) with AMI are being admitted to relatively unsophisticated hospitals, while Wright et al showed that 35.5% of patients with AMI were admitted to relatively unsophisticated hospitals [64].

The relationship between accessibility to services and patient outcome may be important in the private sector as well. In this era of emphasis on reducing costs, increasing efficiency, and preserving quality of care, health care is becoming more regionalized as health-care facilities have begun to consolidate. "Centers of excellence" – i.e., discrete centers which harbor specialized medical technologies necessary for various medical interventions, to which other facilities must refer —have become the regional mainstay for delivering advanced care. Concern arises that this trend may limit equal access of technology to all patients and may affect patient outcome [64] . Hence, the relationship between resources and patient outcome is one which has not been fully established and requires further investigation.

B. Thrombolytics

Thrombolytic usage increased with decreasing level of sophistication (p=0.026). This result is concordant with low rates of PTCA in the hospitals with high rates of thrombolysis. Thrombolytic use remained relatively uniform from 1993-1997. p(trend)=0.071. Over time, group 1 (p(trend)=0.006) and group 3 hospitals (p(trend)=0.005) showed a significant decrease in the use of thrombolytics, whereas increased use was found in group 2 hospitals (p(trend)= 0.001).

C. Pharmacology

The results of Wright et al. suggest that "on-site cardiac technology may be a measure of a hospital's 'total treatment effect' received by patients initially admitted to these facilities for which revascularization procedures are but one indicator." [64] If this were true, differences should be observed not only in procedural care of patients but also in pharmacologic treatment of patients, depending on hospital sophistication. In our analysis, however, significant trends in medication use were uniform among hospital types (figures 18, 21, 24, 36).

Medication utilization trends from 1993-1997 show a significant increase in the use of ACE inhibitors (figure 16), beta-blockers (figure 19),and lipid lowering agents (figure

34), as well as a significant decrease in the use of calcium channel blockers (figure 22). These trends conform to the guidelines developed from published clinical trials that were carried out during the time period under investigation. As mentioned above, these trends were seen in all hospital groups indicating that, with regard to pharmacologic treatment, clinical trial results are being translated into patient care in all VA hospitals, independent of "on-site cardiac technology."

ACE inhibitor use significantly increased by 64% from 1993 (26.43%) to 1997 (43.38%) (p=0.001), reflecting evidence from clinical trials that ACE inhibitors increase both short-term and long-term survival in AMI patients [23, 24, 42-44]. This trend was observed in all hospital groups (figure 18).

Similarly, the use of beta-blockers increased by 25% from 1993 (63.43%) to 1997 (79.19%) (p=0.001). This increasing trend was also seen in all hospital groups (figure 21) reflects the results of clinical trials that show that beta-blockers reduce morbidity and mortality following AMI [39-41].

Most impressive, utilization of hypolipidemic agents increased by 350% from 1993 (8.71%) to 1997 (39.22%) (p=0.001). This increase reflects the results of recent trials that show that substantially lowering cholesterol levels in patients at high risk for coronary heart disease and in patients with established but stable heart disease, reduces cardiovascular morbidity and mortality [57-59]. This increasing trend was also found in all hospital groups (figure 36).

Calcium channel blocker use decreased by 45% from 1993 (32.29%) to 1997 (17.75%), as no studies support the use of these agents in early treatment of AMI or in secondary prevention for most AMI patients. In fact, in some patients this class of drugs may be harmful and can exacerbate ischemia and cause death from myocardial depression or reflex tachycardia [45-49]. This decreasing trend was seen in all hospital groups (figure 24).

Our data suggest a downward trend in digitalis use from 1993 (8.71%) to 1997 (6.73%) (p=0.124), reflecting recent evidence that digitalis may not reduce total mortality following AMI [56] and is recommended only in patients who have supraventricular arrhythmias or CHF that is not responsive to ACE inhibitors or diuretics [1]. This trend was significant, however, only in group 3 hospitals (p=0.007) (figure 27).

Despite the uniform trends seen in all hospital groups with regard to medication usage over time, significant differences were observed in the rates of beta-blocker and hypolipidemic agent utilization among hospital groups (figures 20 and 35). Although utilization over time did increase for both beta-blockers and hypolipidemic agents in all hospital groups, group 1 hospitals had significantly lower usage of both these agents when compared with the more sophisticated hospital groups (p=0.001 for both medications). Hence, unsophisticated hospitals may need to further increase their use of beta-blockers and hypolipidemic agents.

D. Study Strengths

One of the main strengths of our study was the six year time span over which data were collected. Employing data from the VA health care system represents an additional strength when analyzing rates of procedure use, as issues of patient insurance affecting procedure availability or provider-driven induced demand are not of concern. In the VA system all veterans eligible for VA care can obtain procedures independent of financial status. Additionally, since VA physicians are salaried, physician driven-induced demand does not contribute to rates of procedure use across hospital types. [64].

E. Study Limitations

It is important to note that this is an observational study with certain limitations that will need to be resolved with subsequent analyses and further investigation before the clinical implications can be firmly established. Although did not adjust for varied patient characteristics and severity of patient illness across hospital groups, crude analyses reflect that patient characteristics (i.e., systolic hypertension, diastolic hypertension, Q-wave MI,

significant CHF, ischemia post-MI, arrhythmia, Caucasian race, prior MI, history of smoking, diabetes, age >60) did not differ significantly by hospital sophistication level (data not shown).

In addition, we did not control for the fact that the severity of patient illness may have differed according to year of hospital study. Other clinical trials being conducted at the same time as the CHAMP study may have led to a competition for patients, and depending on which trial was being conducted each year, CHAMP may have randomized sicker patients some years than others.

F. Conclusion

Overall, analysis of CABG and PTCA utilization rates reveals differences over time and according to hospital sophistication. These results highlight the need for outcome analyses, as the impact of these findings will be better understood when outcome analyses are performed. Results of these analyses may have far-reaching effects on efforts to regionalize heath care in both the VA health care system and the private sector. With regard to pharmacologic interventions, it appears that trends in treatment are rather uniform across different hospital types and follow the results of clinical trials. Since clinical trial results are ultimately translated into guidelines, our data suggest that, over time, the trends in the pharmacologic care delivered by our country's largest HMO, the VA system, to patients diagnosed with AMI, adhere to the AHA/ACC clinical guidelines that were designated to provide standards for optimum patient care.

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VII. Figure References and Legends

- **Group 1**
  No Cardiac Cath Lab
- **Group 2**
  Cardiac Cath Lab
  No Cardiac Surgery
- **Group 3**
  Cardiac Surgery

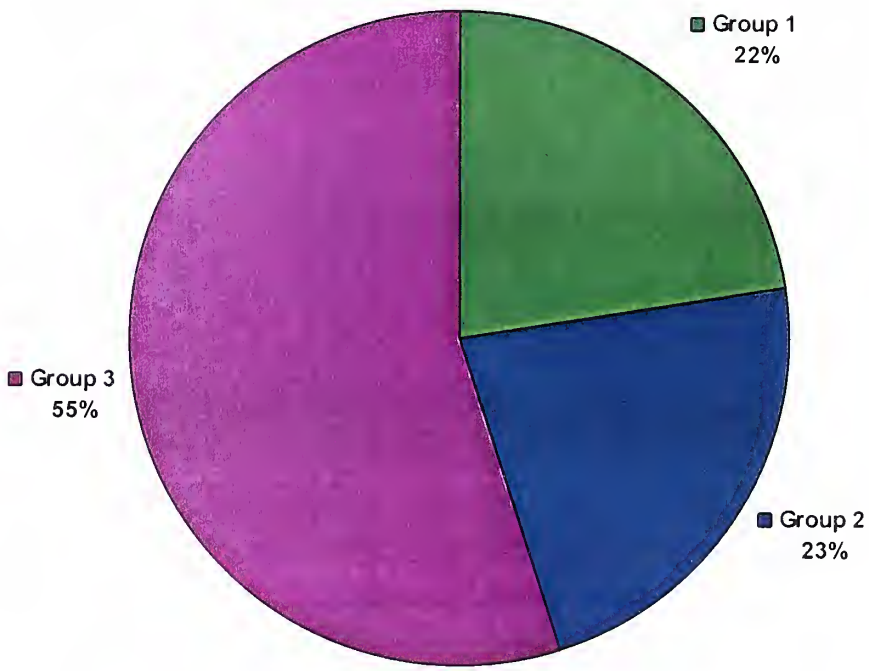

Figure 1. CHAMP Enrollment by Hospital Cardiac Capability. This pie chart depicts the percent of total patients randomized into CHAMP that were initially admitted to each of the three hospital types. The three hospital types are distinguished by sophistication level.

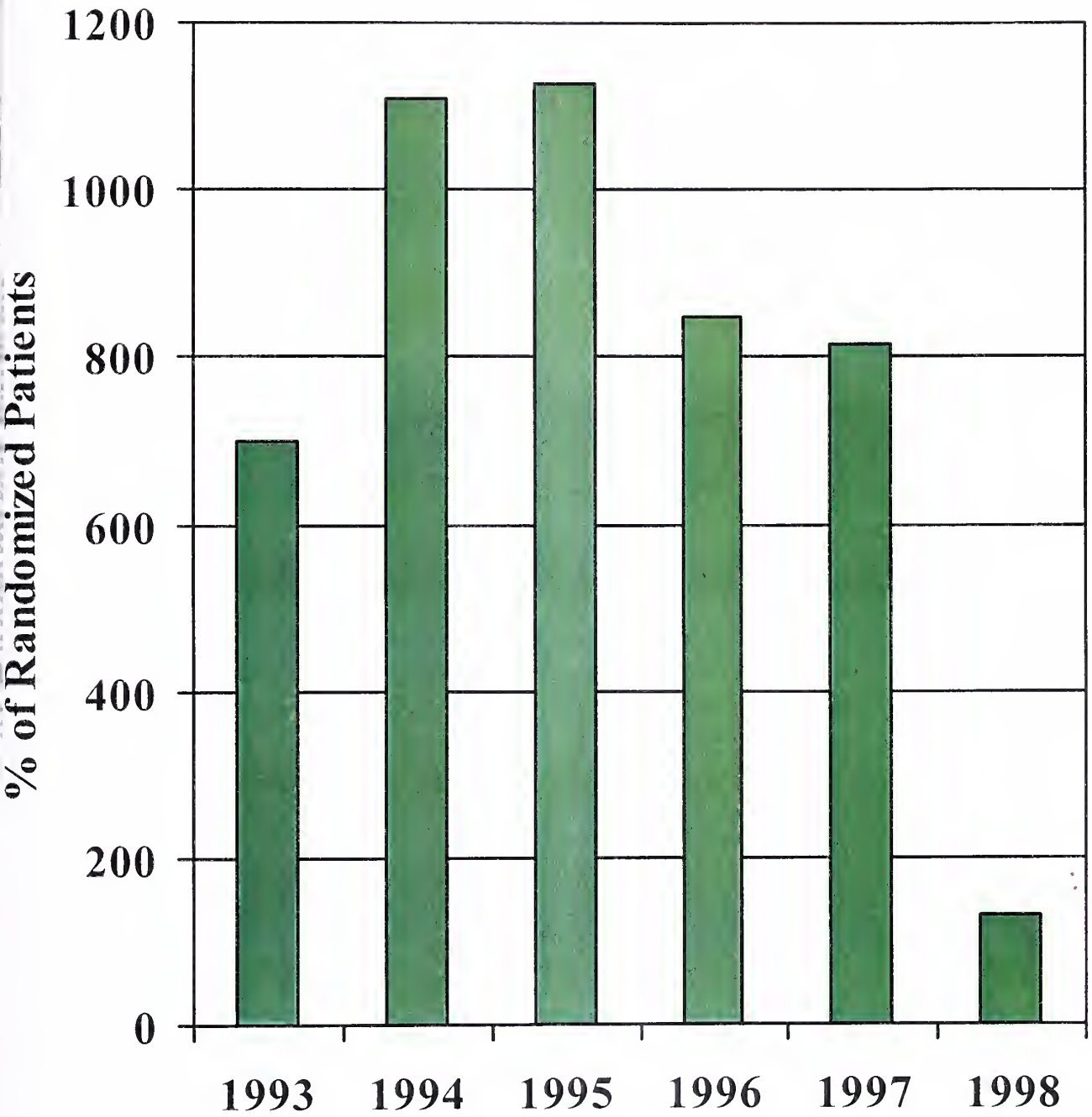

Figure 2. CHAMP Enrollment 1993-1998. This graph depicts the percent of total patients randomized into the CHAMP study that were enrolled each year under investigation.

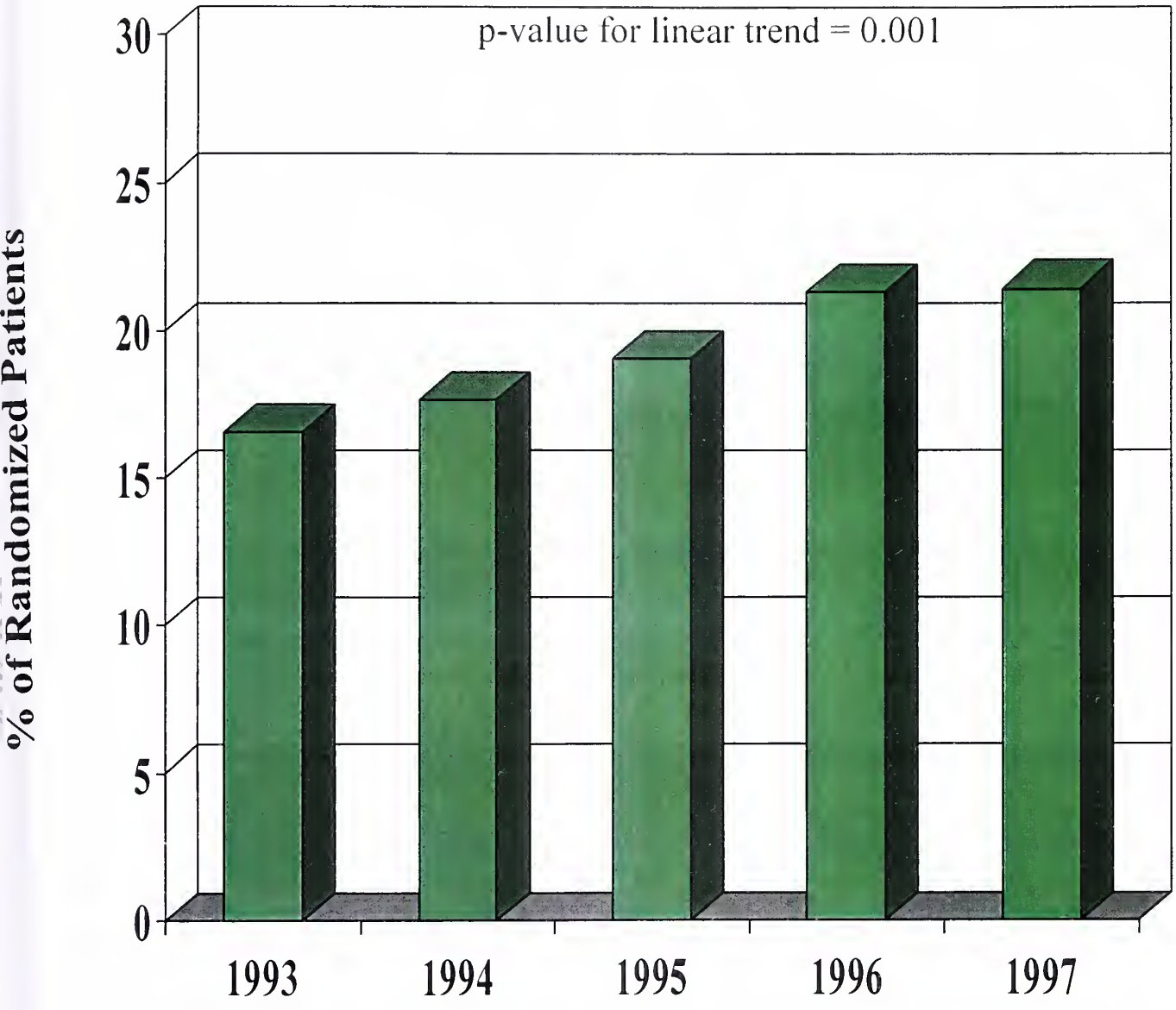

Figure 3. Total CABG (Within 90 Days) Post-MI by Year. This graph depicts the percent of patients randomized into the CHAMP study that were treated with cardiac surgery for each year under investigation.

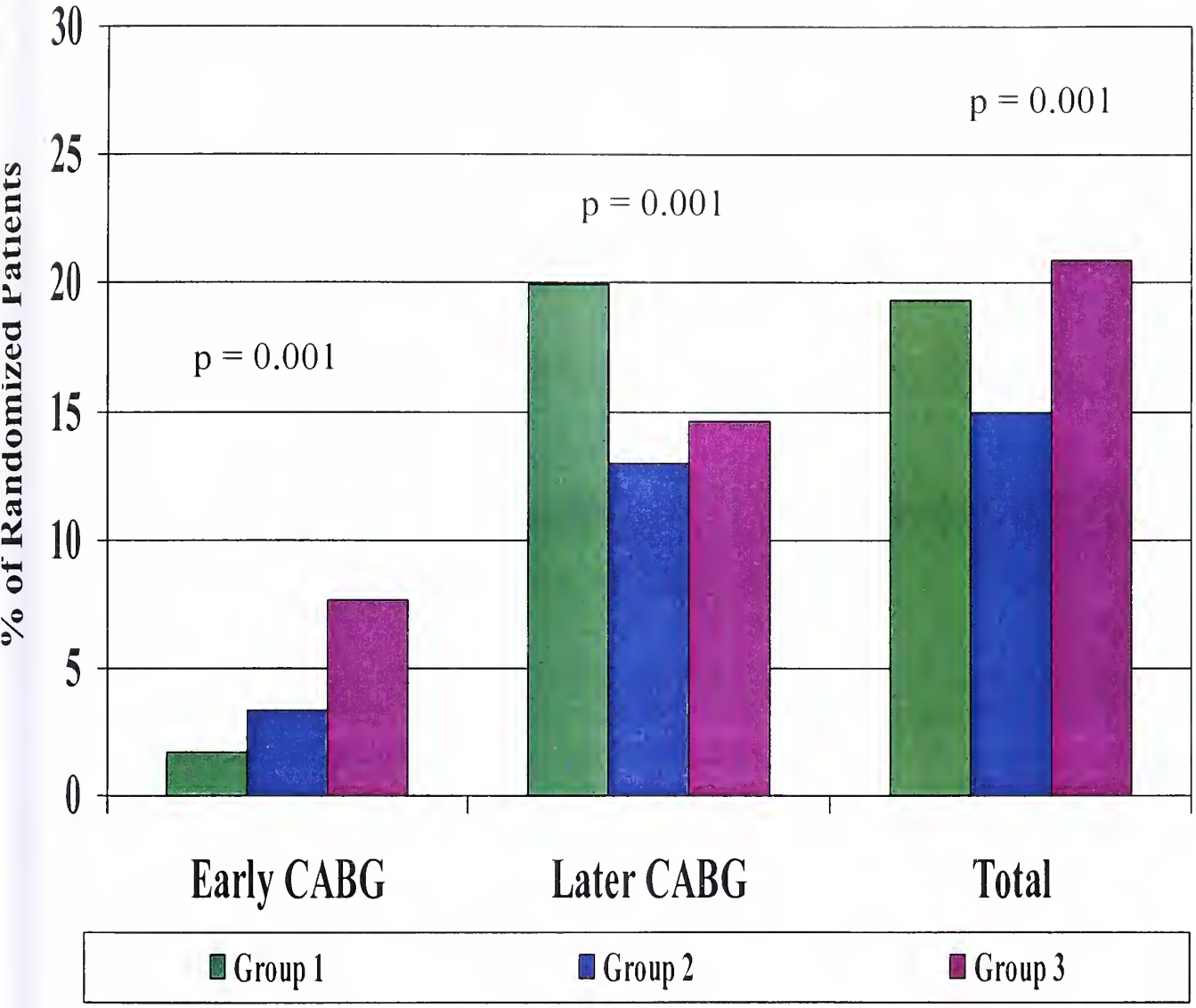

Figure 4. Early (Within 14 Days) vs. Later (Between 14-90 Days) CABG Post-MI by Hospital Type. This graph depicts the percent of CHAMP study patients that underwent cardiac surgery within 14 days of index MI and the percent that underwent cardiac surgery between 14 - 90 days after index MI as well as the total percent of patients that underwent cardiac surgery within 90 days of infarct MI.

p-value for linear trend

Group 1	p = 0.233
Group 2	p = 0.021
Group 3	p = 0.001

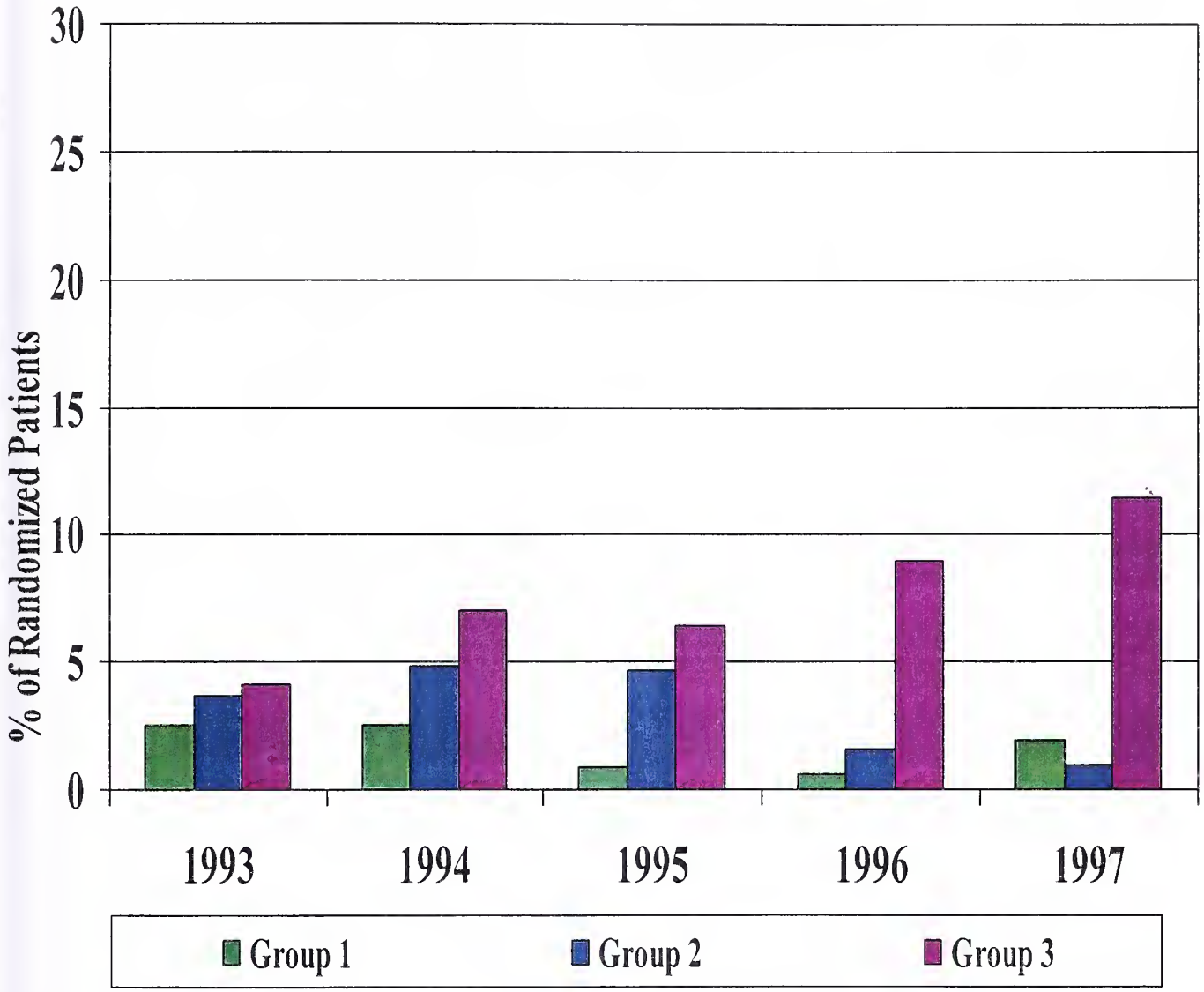

Figure 5. Early CABG (Within 14 Days Post-MI) by Hospital Type by Year. This graph depicts the percent of CHAMP study patients that were treated with "early" CABG.

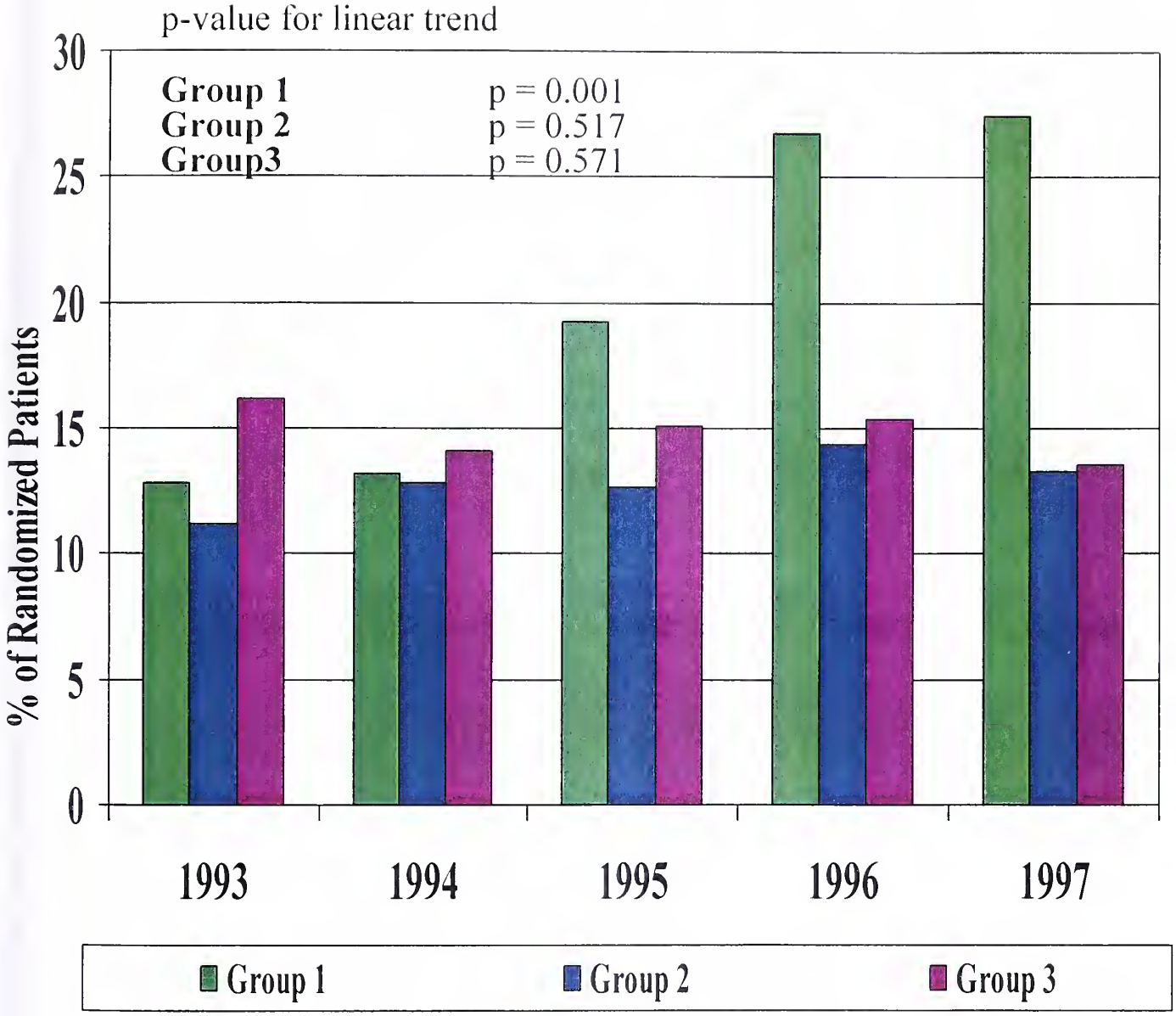

Figure 6. Later CABG (Between 14-90 Days) Post-MI by Hospital Type by Year. This graph depicts the percent of CHAMP study patients that were treated with "later" CABG.

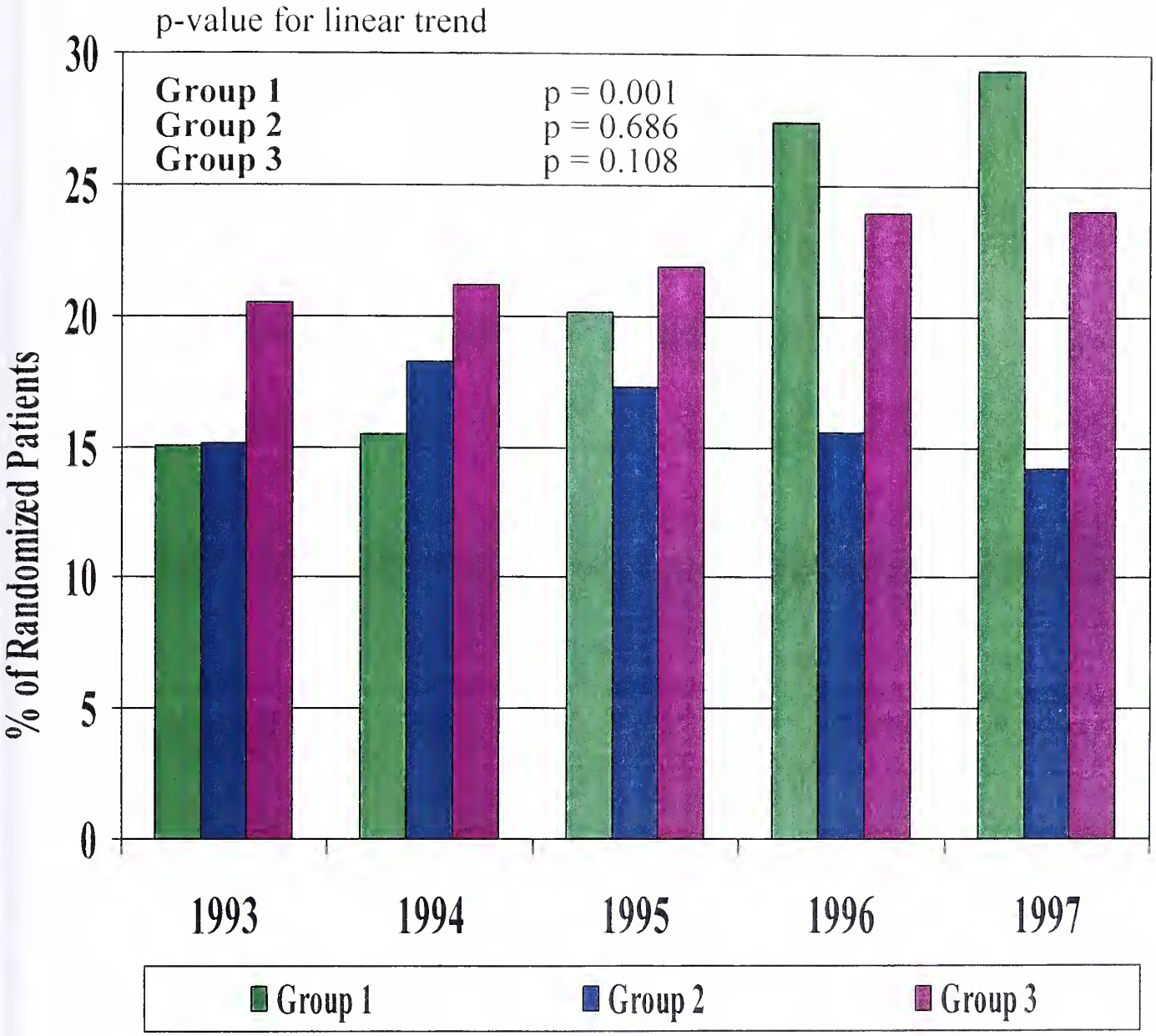

Figure 7. Total CABG (Within 90 Days) Post-MI by Hospital Type by Year. This graph depicts the percent of CHAMP study patients treated with CABG within 90 days after index MI.

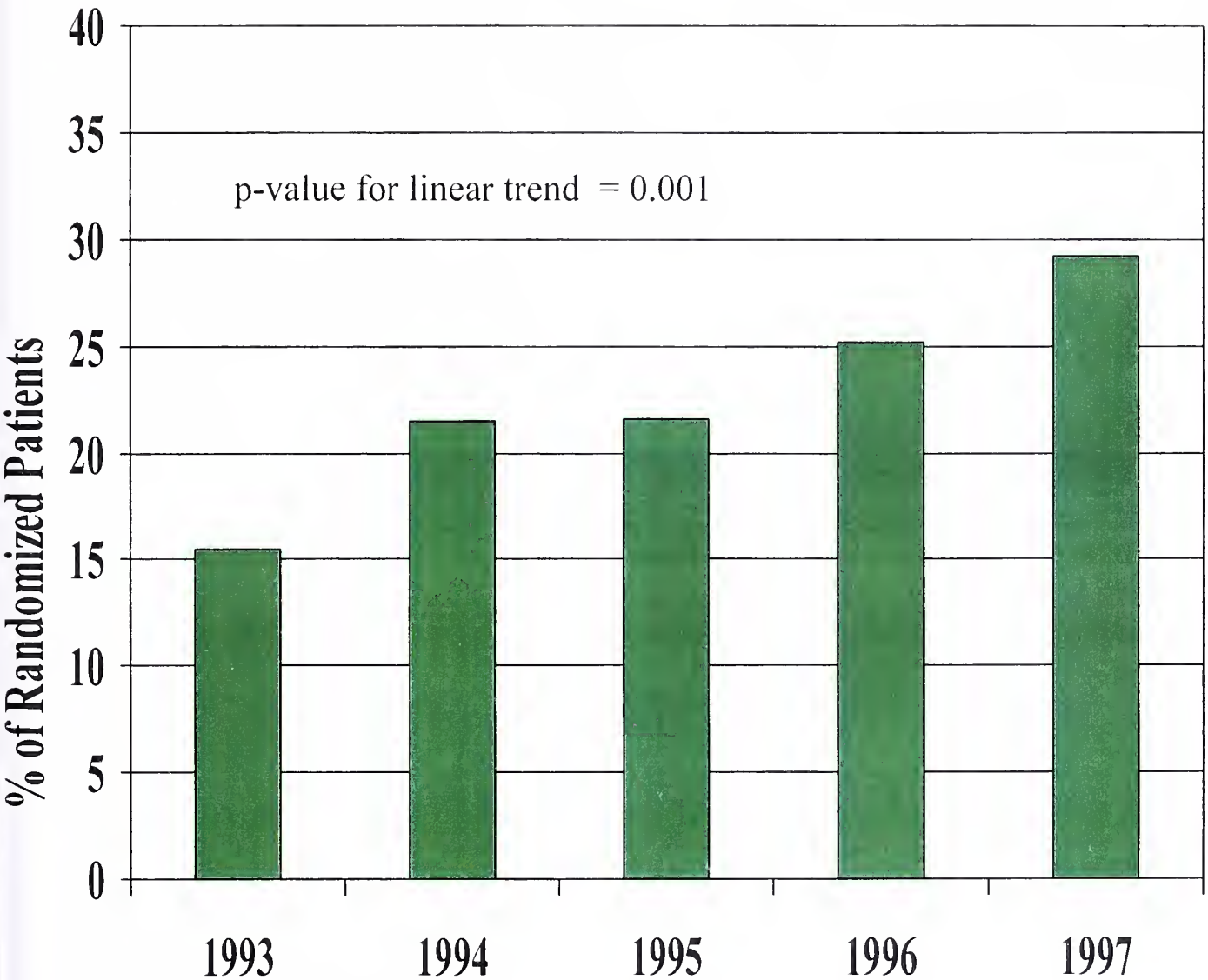

Figure 8. Total PTCA (Within 90 days) Post-MI by Year. This graph depicts the percent of CHAMP study patients that were treated with PTCA within 90 days of infarct MI for each year under investigation.

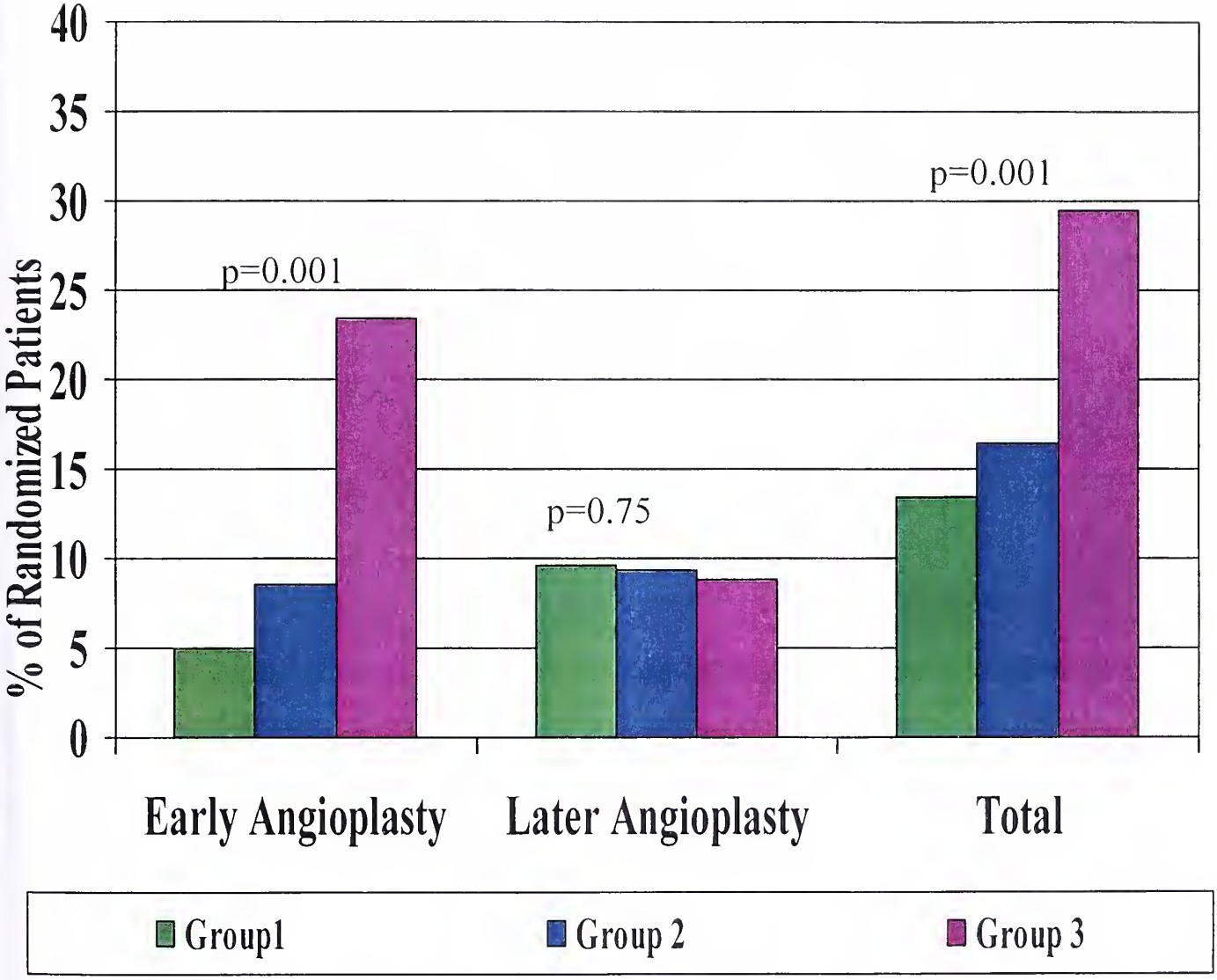

Figure 9. Early (Within 14 days) vs. Later (Between 14-90 Days) PTCA Post-MI by Hospital Type. This graph depicts the percent of CHAMP study patients treated with "early" or "later" PTCA as well as the total percent of patients that underwent PTCA within 90 days of index MI.

p-value for linear trend

Group 1	p=0.366
Group 2	p=0.006
Group 3	p=0.001

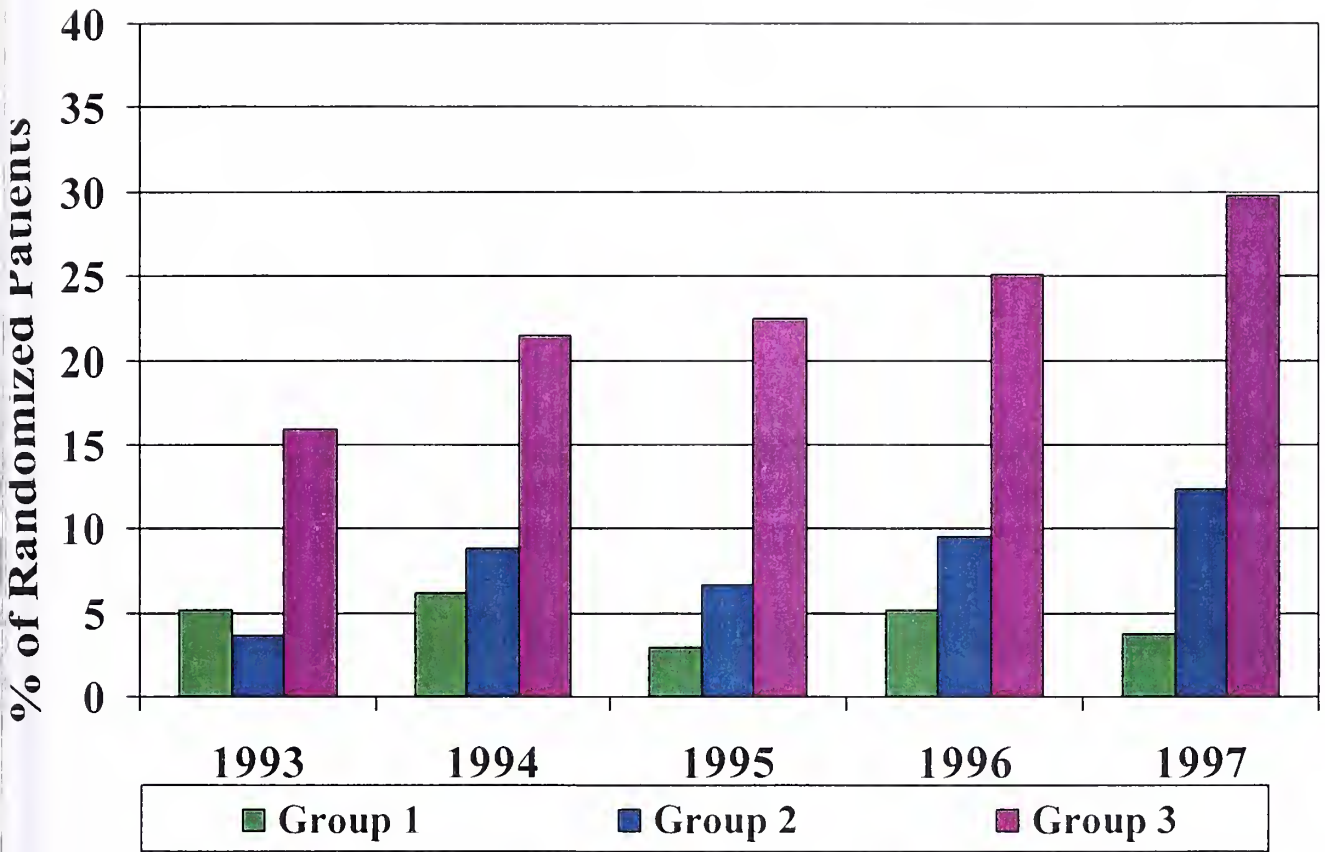

Figure 10. Early PTCA (Within 14 Days) Post-MI by Hospital Type by Year. This graph depicts the percent of CHAMP study patients treated with "early" PTCA.

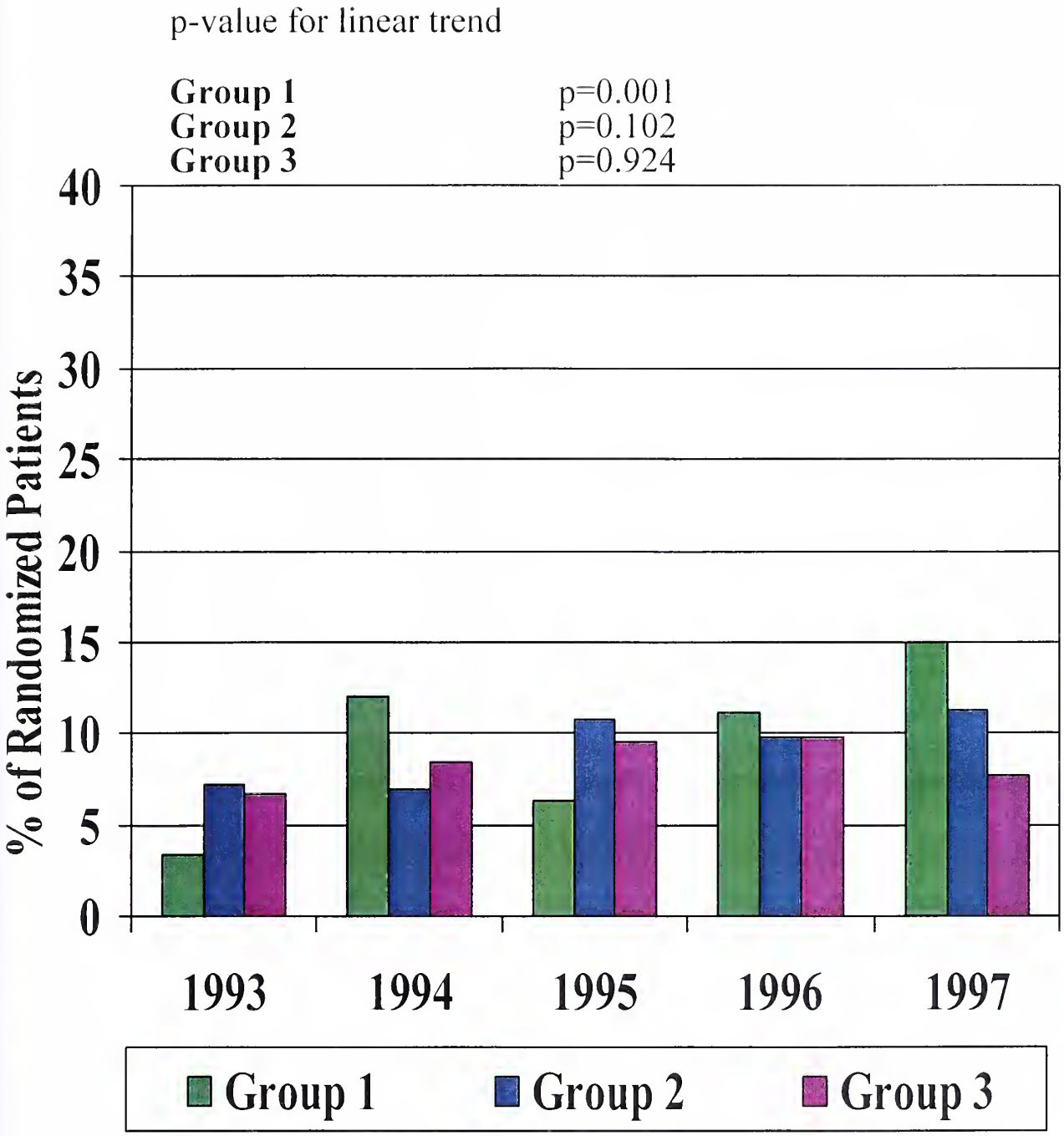

Figure 11. Later PTCA (Between 14-90 Days) Post-MI by Hospital Type by Year. This graph depicts the percent of CHAMP study patients treated with "later" PTCA.

p-value for linear trend

Group 1	p=0.005
Group 2	p=0.001
Group 3	p=0.001

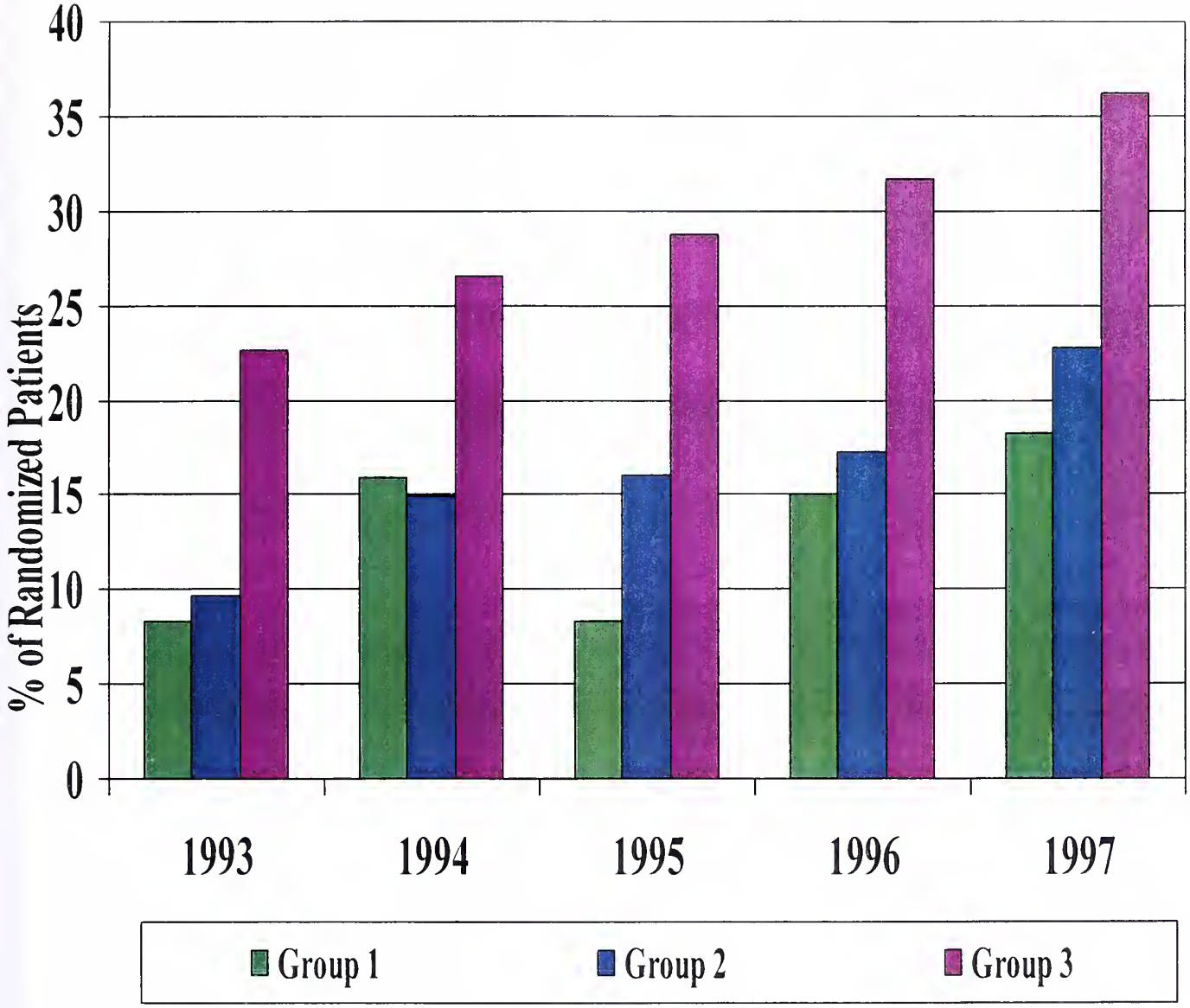

Figure 12. Total PTCA (Within 90 Days) Post-MI by Hospital Type by Year. This graph depicts the percent of CHAMP study patients that were treated with PTCA within 90 days of index MI divided according to the hospital type to which they were admitted and depicted over time.

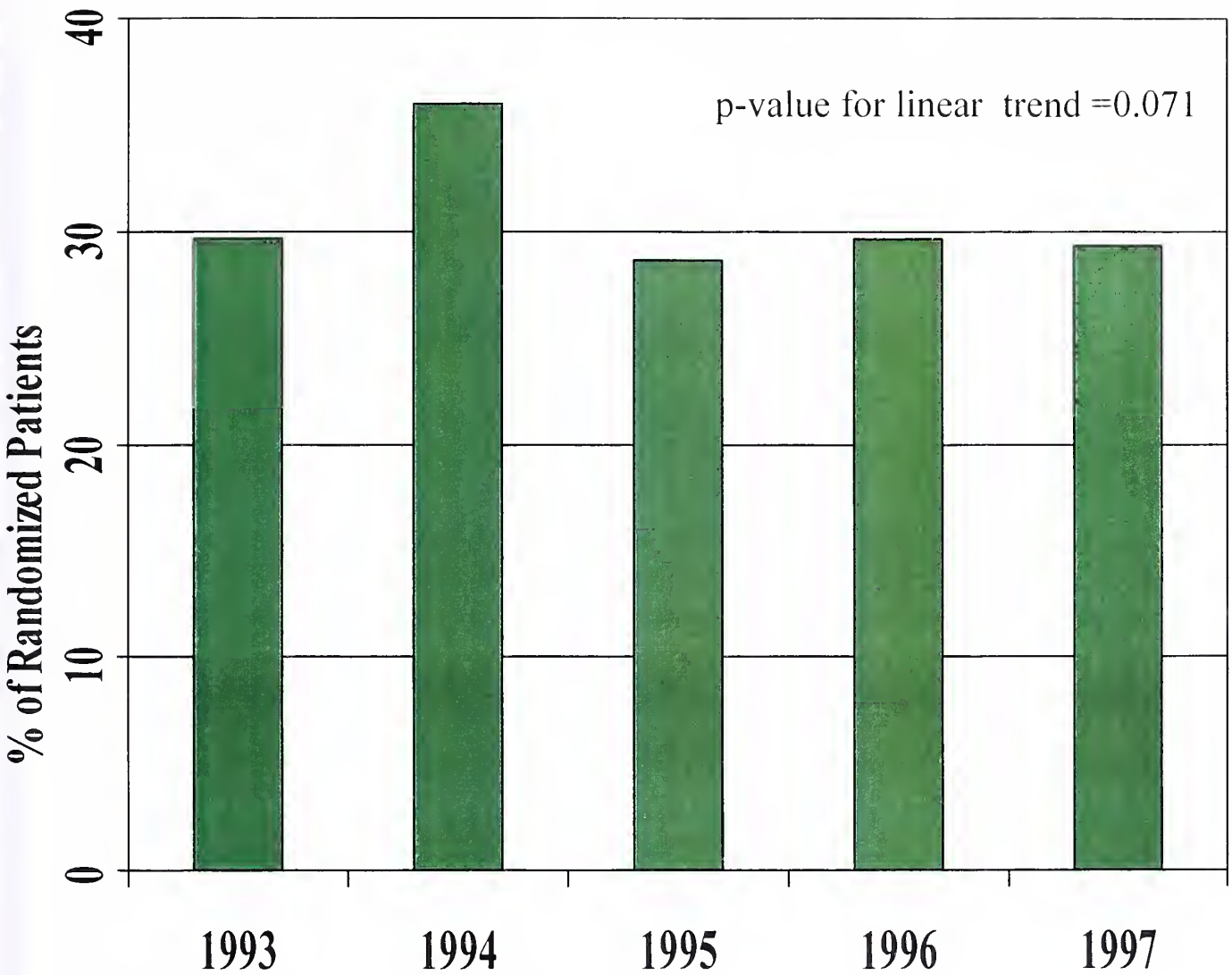

Figure 13. Thrombolytic Use by Year. This graph depicts the percent of CHAMP study patients treated with thrombolytics for each year under investigation.

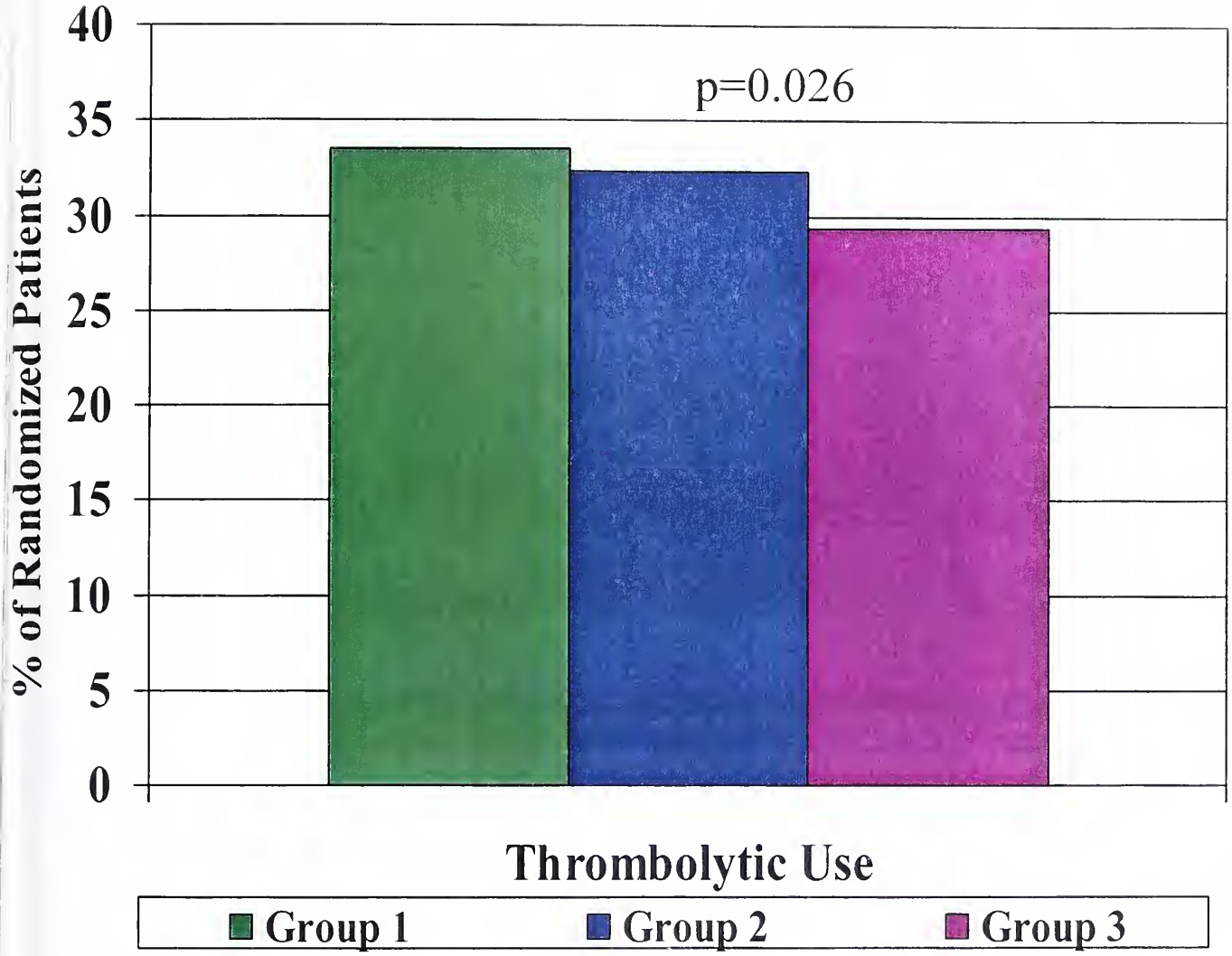

Figure 14. Thrombolytic Use by Hospital Type. This graph depicts the percent of CHAMP study patients treated with thrombolytics divided according to the sophistication level of the hospital to which they were admitted.

p-value for linear trend
Group 1 p=0.006
Group 2 p=0.001
Group 3 p=0.005

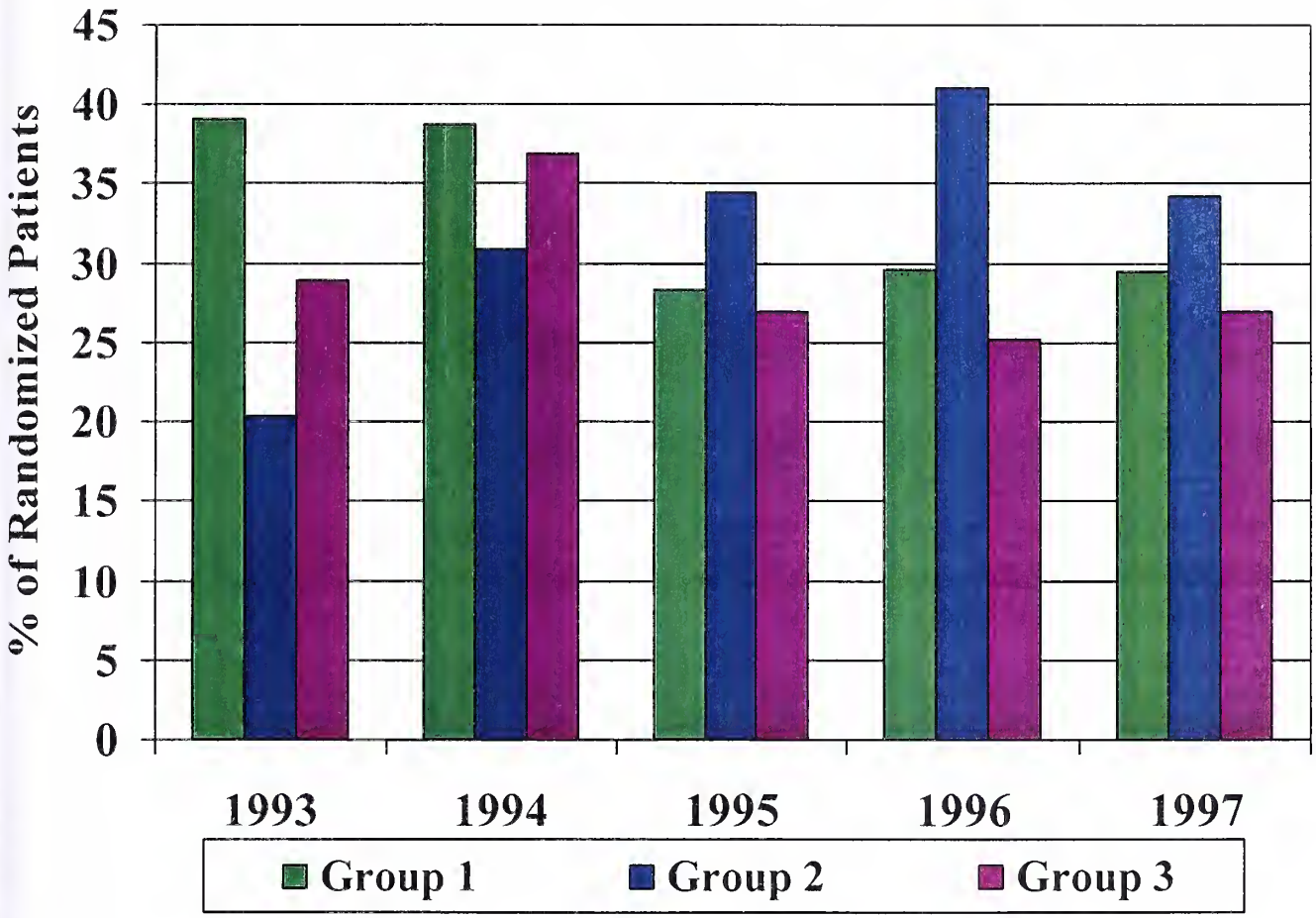

Figure 15. Thrombolytic Use by Hospital Type by Year. This graph depicts the percent of CHAMP study patients treated with thrombolytics divided according to the hospital type to which they were admitted and depicted over time.

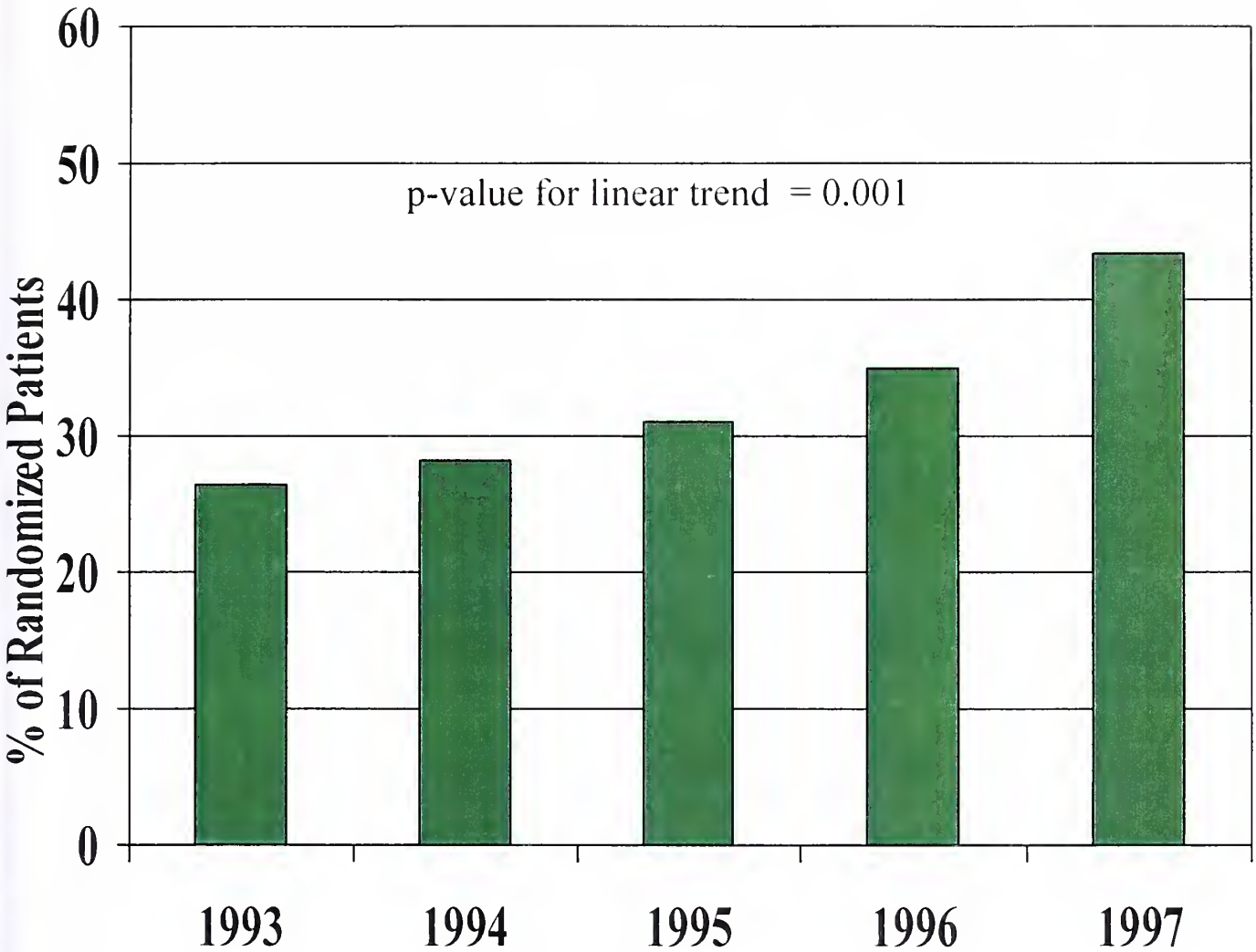

Figure 16. ACE Inhibitor Use by Year. This graph depicts the percent of CHAMP study patients treated with ACE inhibitors for each year under investigation.

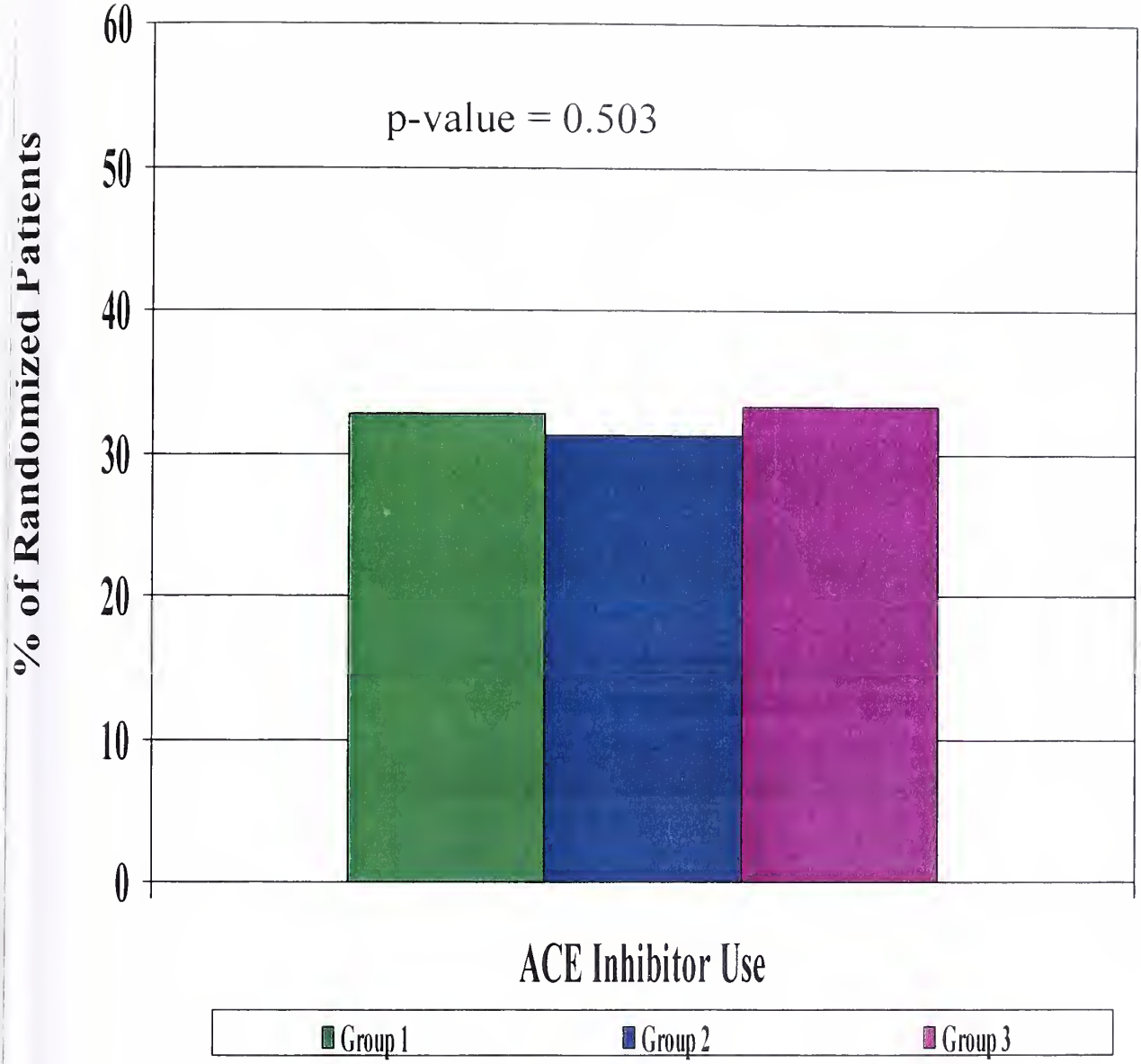

Figure 17. ACE Inhibitor Use by Hospital Type. This graph depicts the percent of CHAMP study patients treated with ACE inhibitors divided according to the hospital type to which they were admitted.

p-value for linear trend

Group 1	p = 0.029
Group 2	p = 0.001
Group 3	p = 0.001

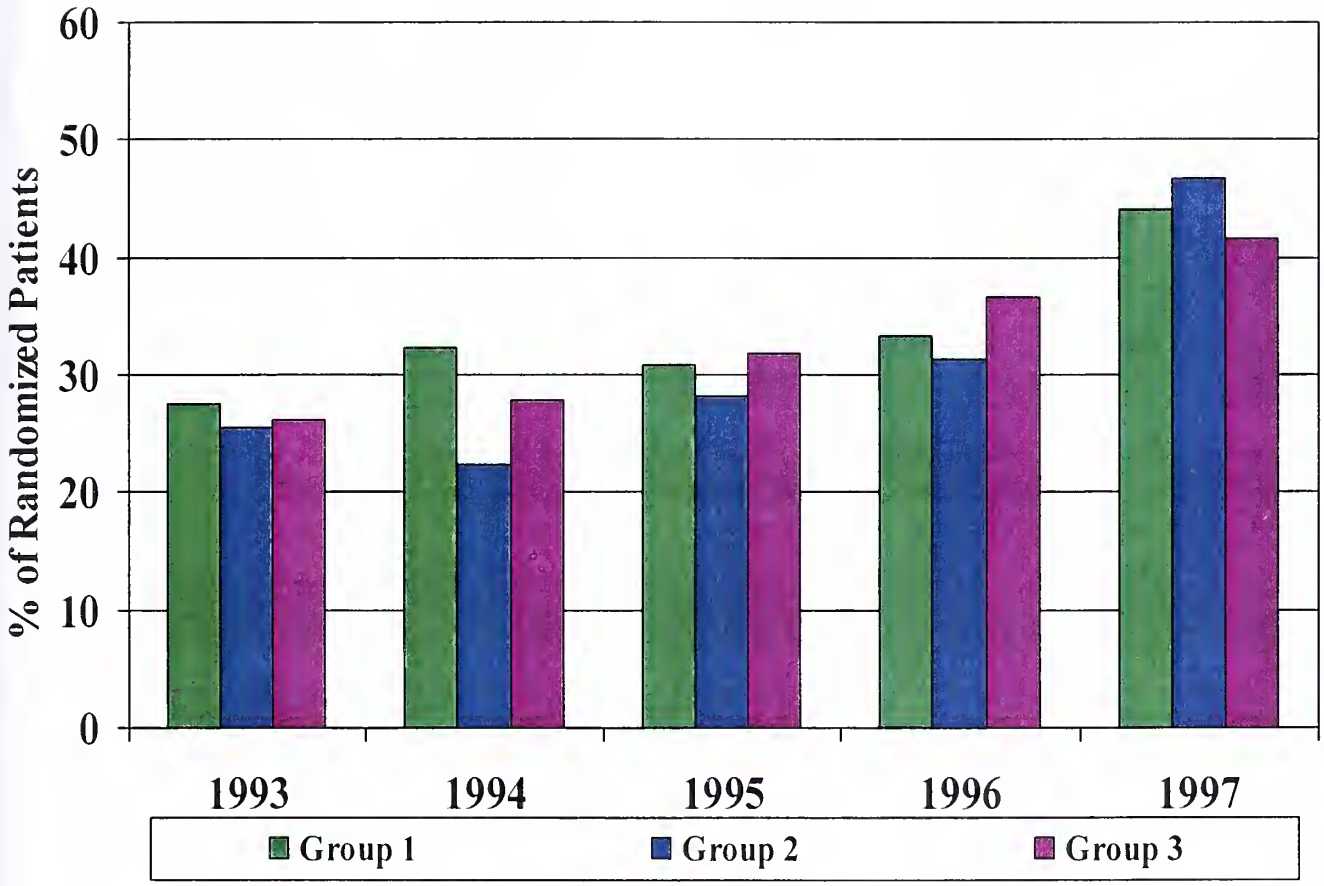

Figure 18. ACE Inhibitor Use by Hospital Type by Year. This graphs depicts the percent of CHAMP study patients treated with ACE inhibitors according to the hospital type to which they were admitted and depicted over time.

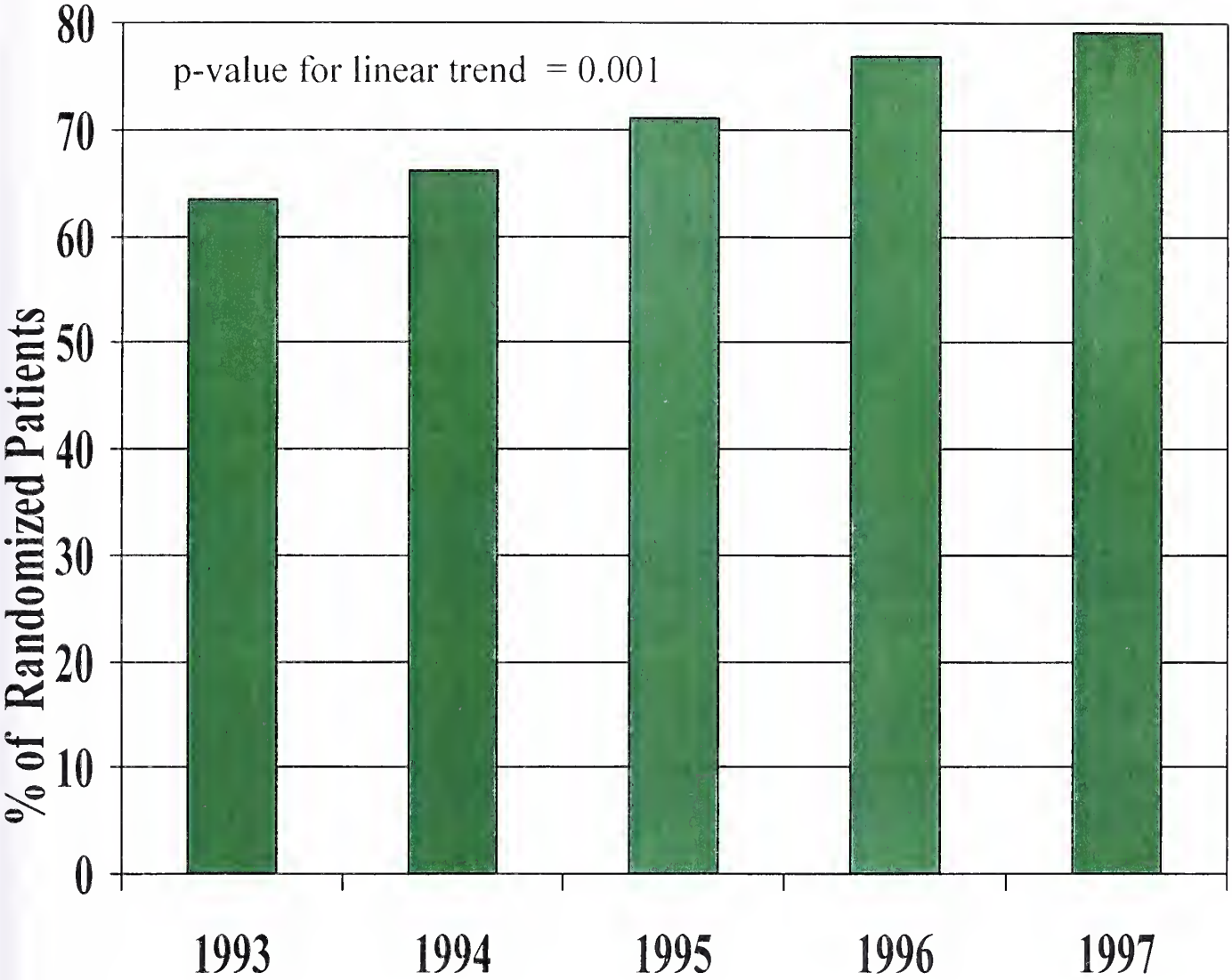

Figure 19. Beta-Blocker Use by Year. This graph depicts the percent of CHAMP study patients treated with beta-blockers for each year under investigation.

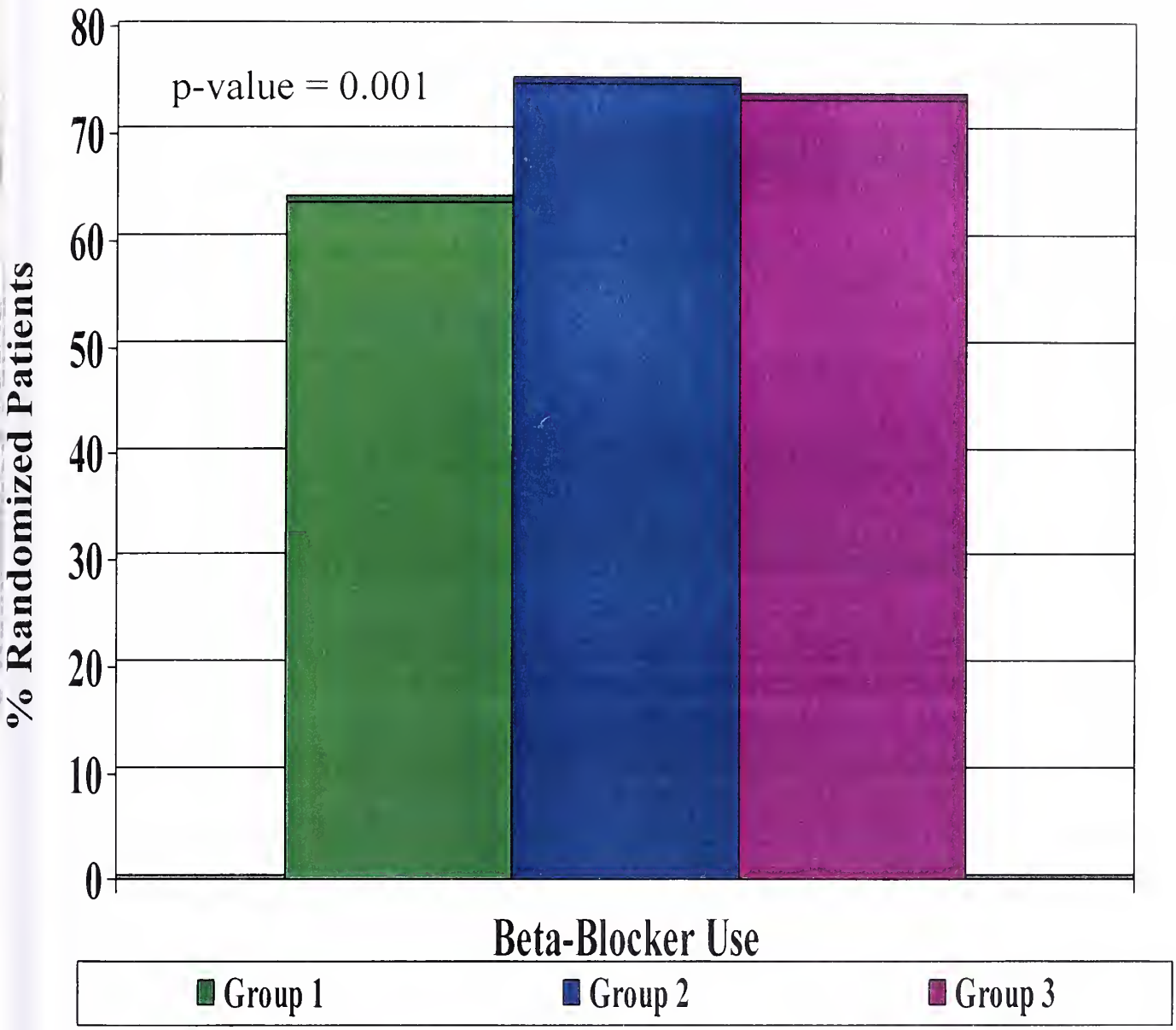

Figure 20. Beta-Blocker Use by Hospital Type. This graph depicts the percent of CHAMP study patients treated with beta-blockers divided according to the hospital type to which they were admitted.

p-value for linear trend

Group 1	p = 0.001
Group 2	p = 0.001
Group 3	p = 0.001

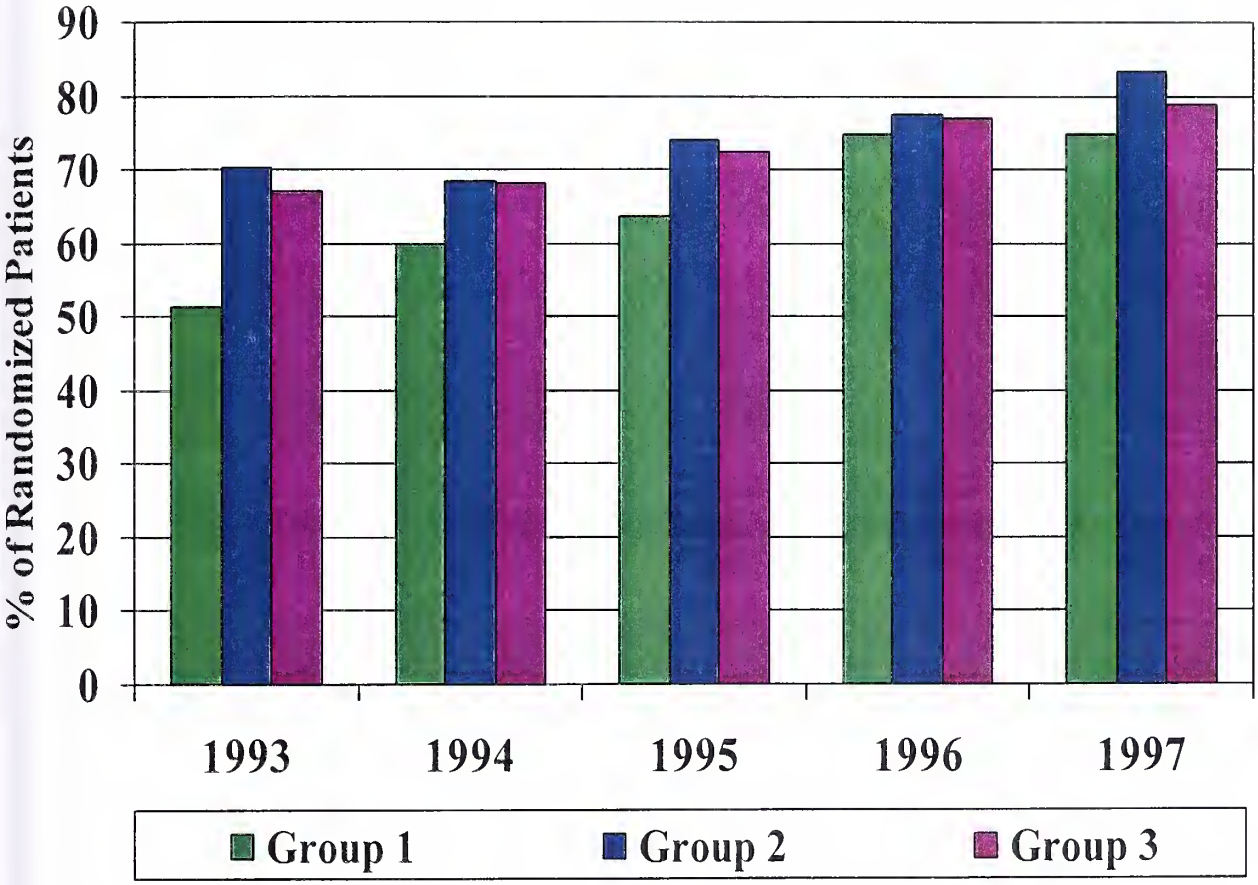

Figure 21. Beta-Blocker Use by Hospital Type by Year. This graphs depicts the percent of CHAMP study patients treated with beta-blockers according to the hospital type to which they were admitted and depicted over time.

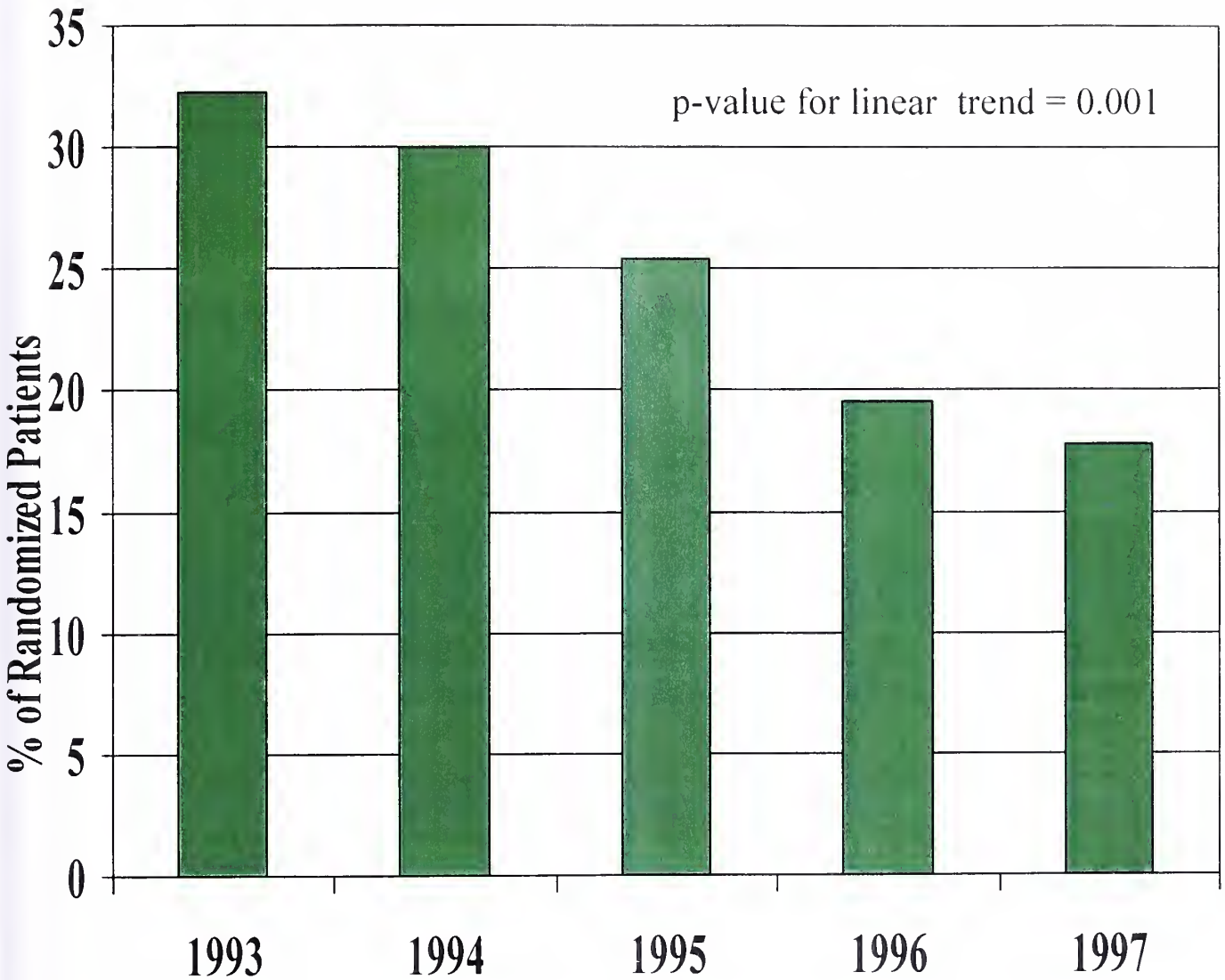

Figure 22. Calcium Channel Blocker Use by Year. This graph depicts the percent of CHAMP study patients treated with calcium channel blockers for each year under investigation.

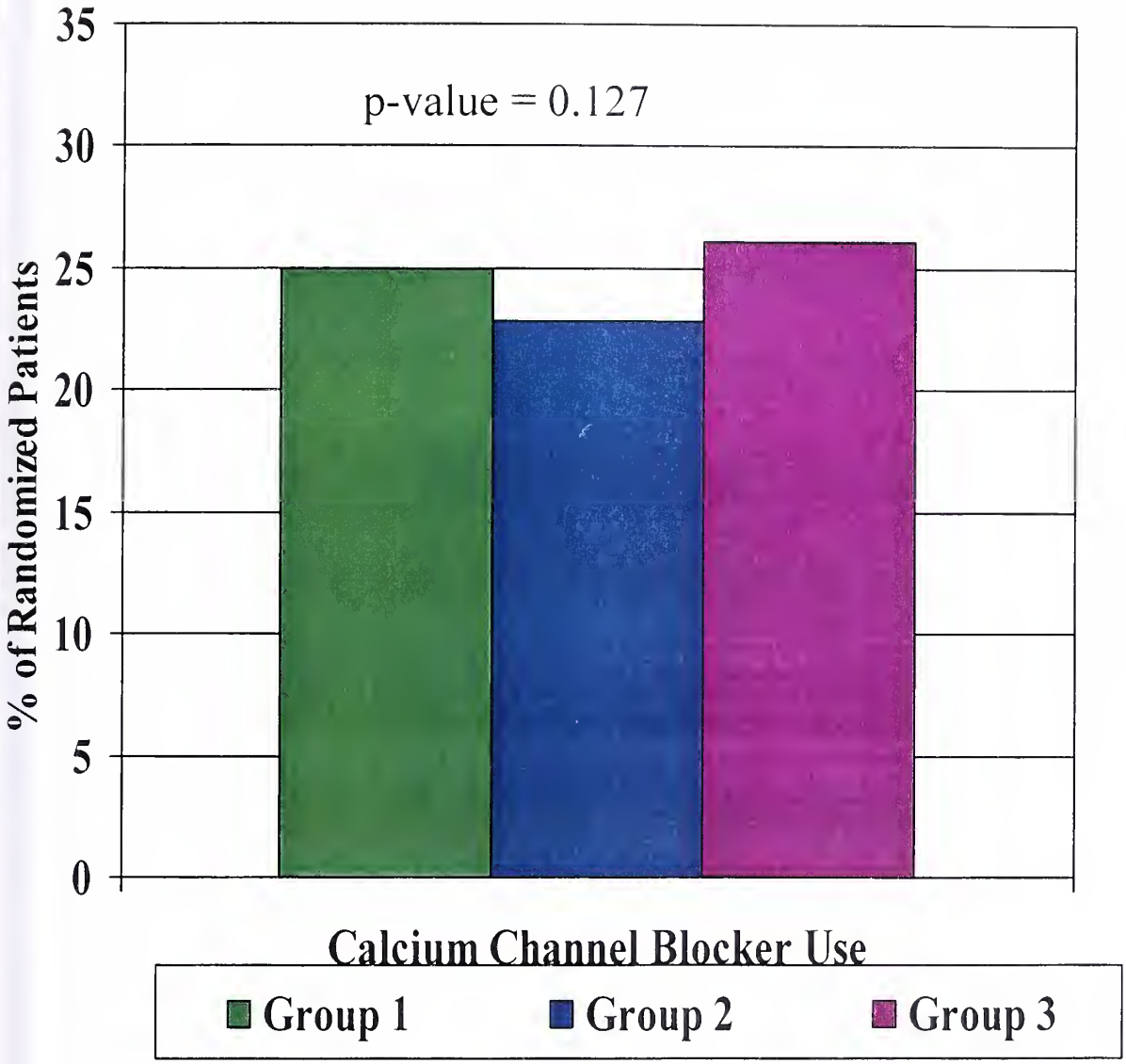

Figure 23. Calcium Channel Blocker Use by Hospital Type. This graph depicts the percent of CHAMP study patients treated with calcium channel blockers divided according to the hospital type to which they were admitted.

p-value for linear trend

Group 1	p = 0.001
Group 2	p = 0.001
Group 3	p = 0.001

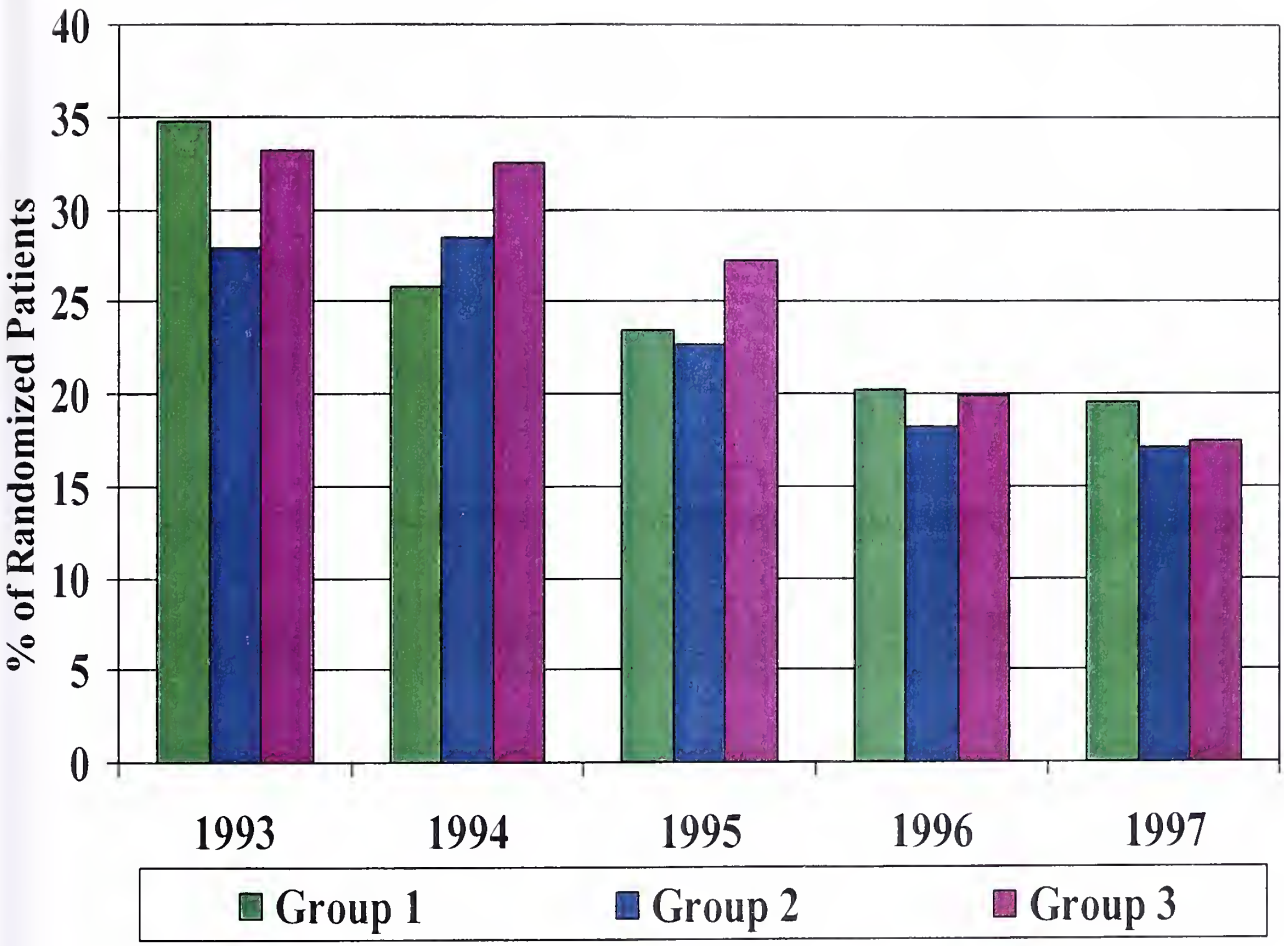

Figure 24. Calcium Channel Blocker Use by Hospital Type by Year. This graphs depicts the percent of CHAMP study patients treated with calcium channel blockers according to the hospital type to which they were admitted and depicted over time.

Figure 25. Digitalis Use by Year. This graph depicts the percent of CHAMP study patients treated with digitalis for each year under investigation.

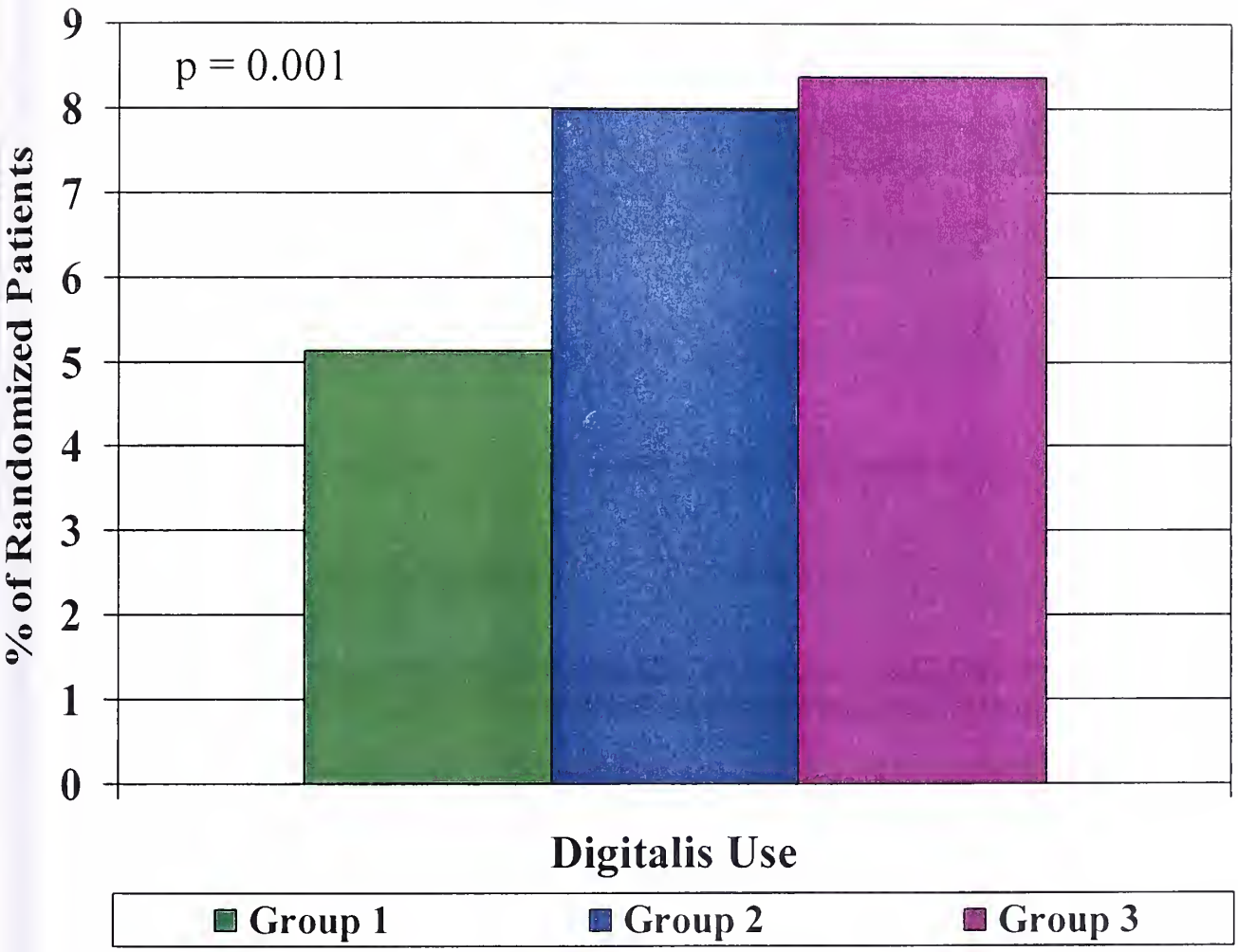

Figure 26. Digitalis Use by Hospital Type. This graph depicts the percent of CHAMP study patients treated with digitalis divided according to the hospital type to which they were admitted.

p-value for linear trend

Group 1	p = 0.077
Group 2	p = 0.851
Group 3	p = 0.007

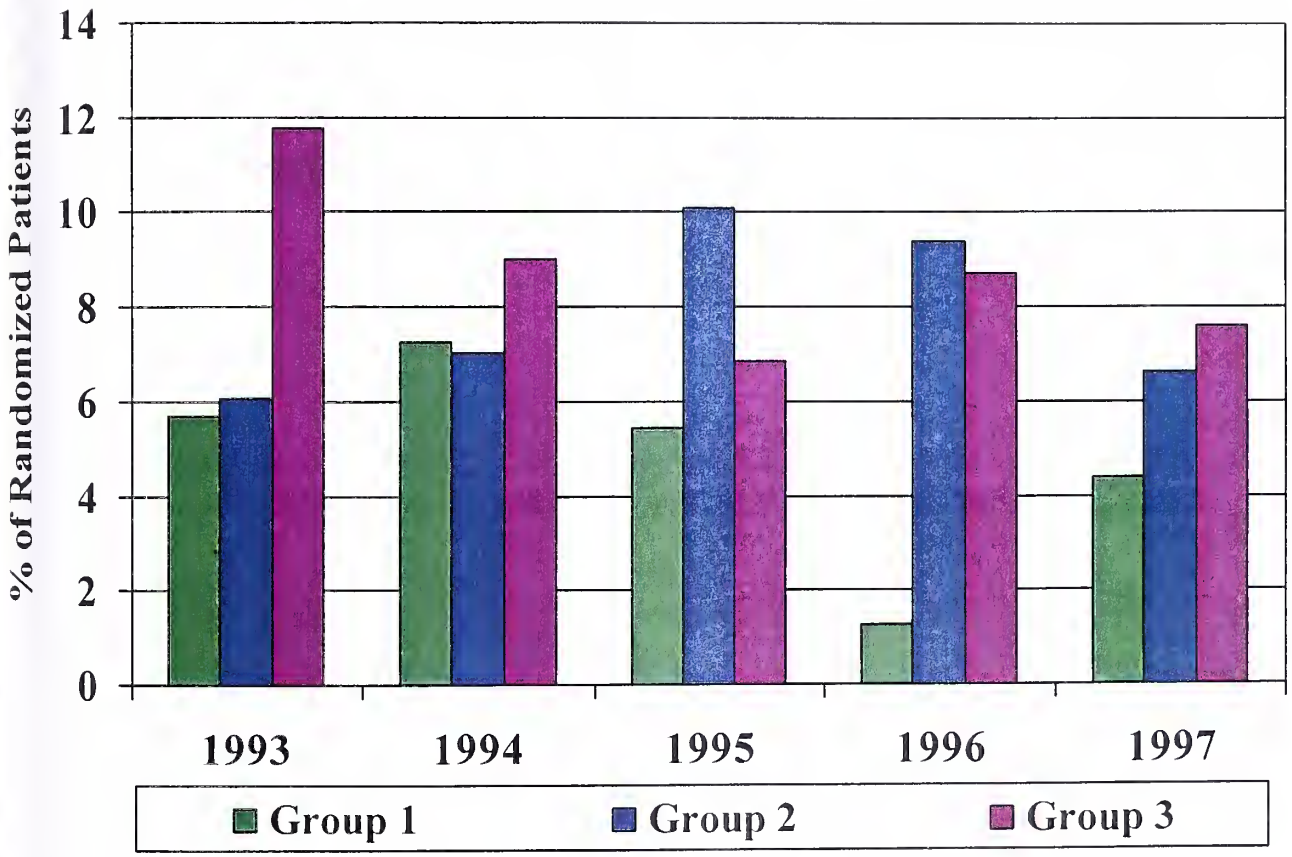

Figure 27. Digitalis Use by Hospital Type by Year. This graphs depicts the percent of CHAMP study patients treated with digitalis according to the hospital type to which they were admitted and depicted over time.

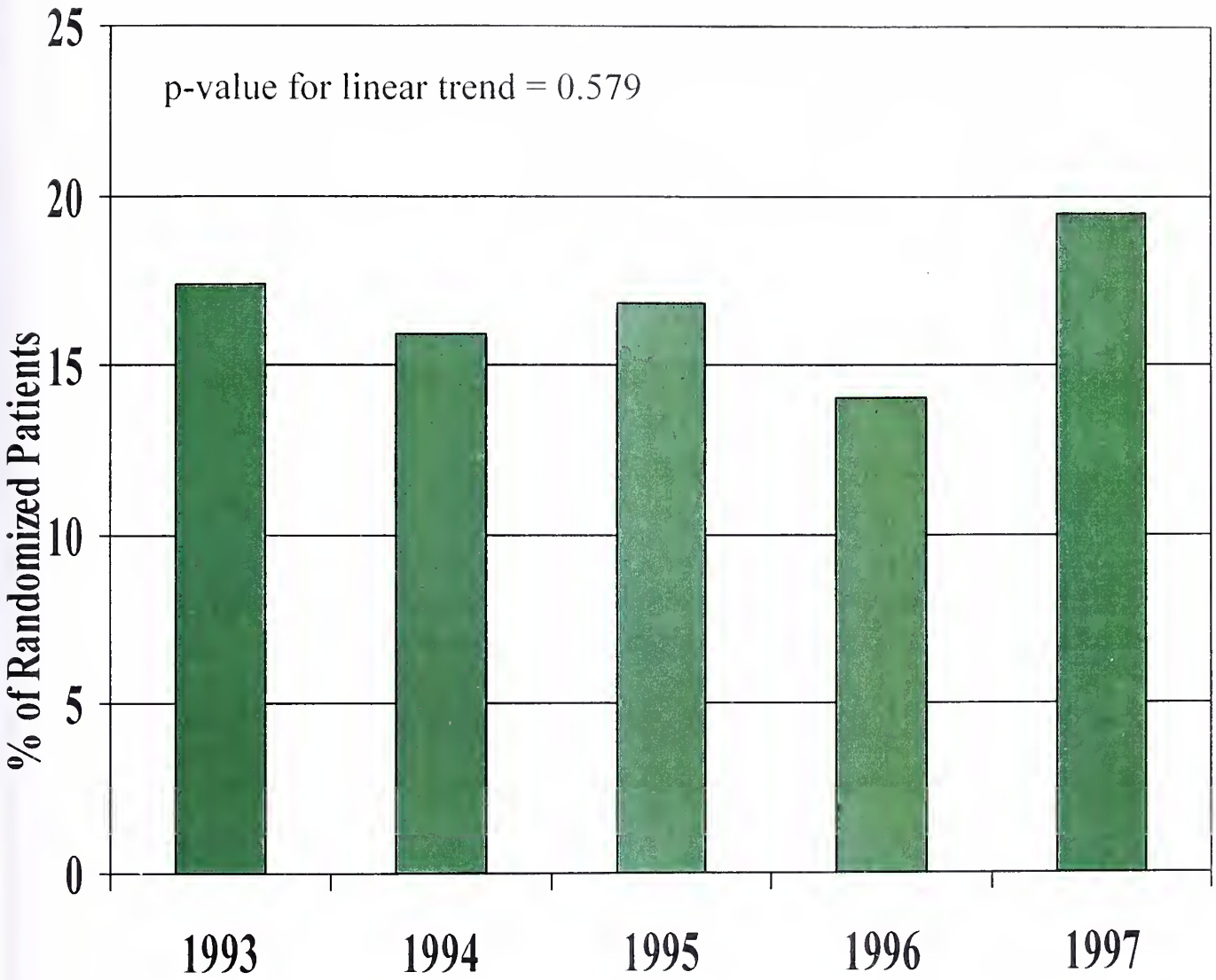

Figure 28. Diuretic Use by Year. This graph depicts the percent of CHAMP study patients treated with diuretics for each year under investigation.

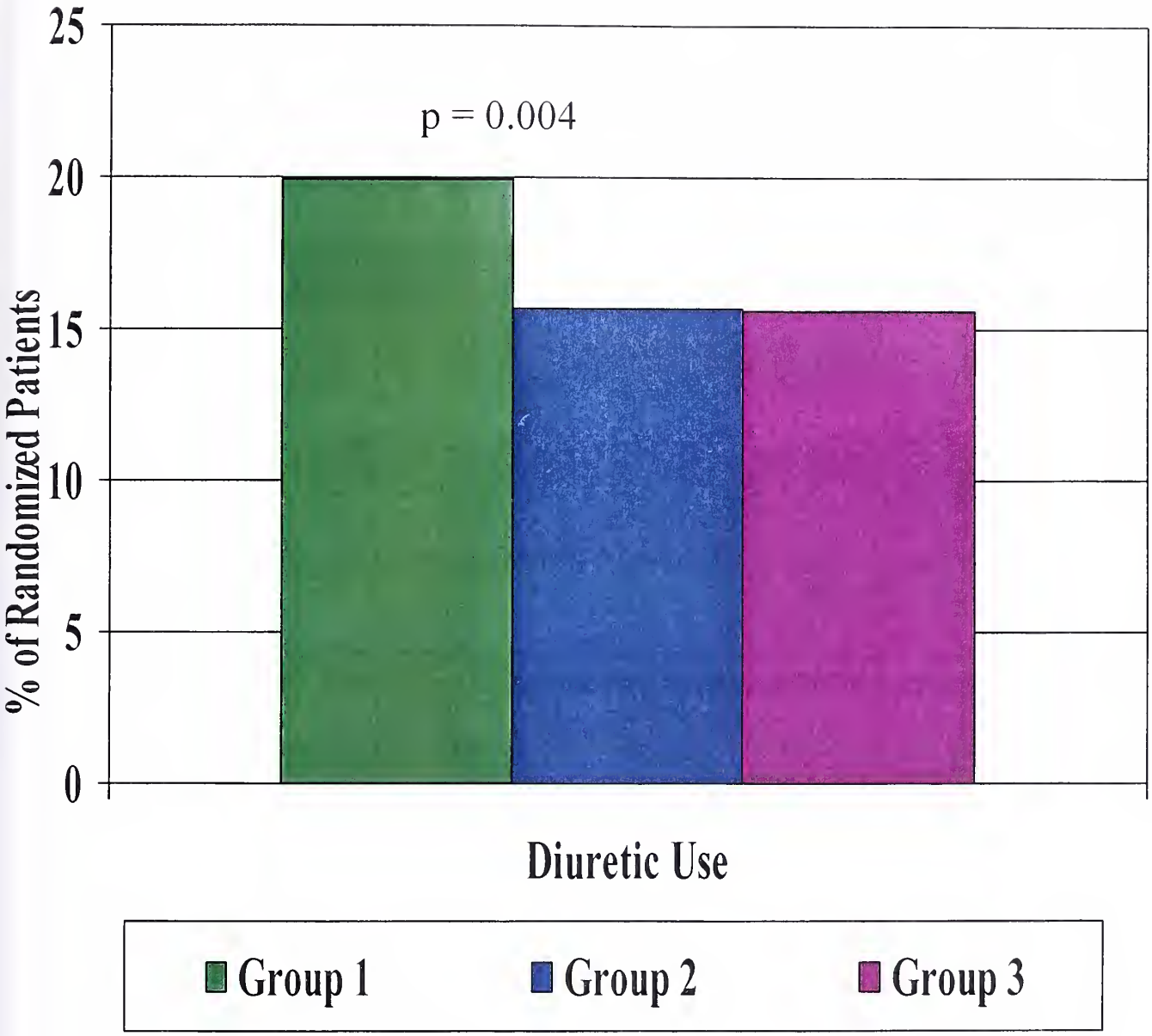

Figure 29. Diuretic Use by Hospital Type. This graph depicts the percent of CHAMP study patients treated with diuretics divided according to the hospital type to which they were admitted.

p-value for linear trend

Group 1	p = 0.212
Group 2	p = 0.895
Group 3	p = 0.966

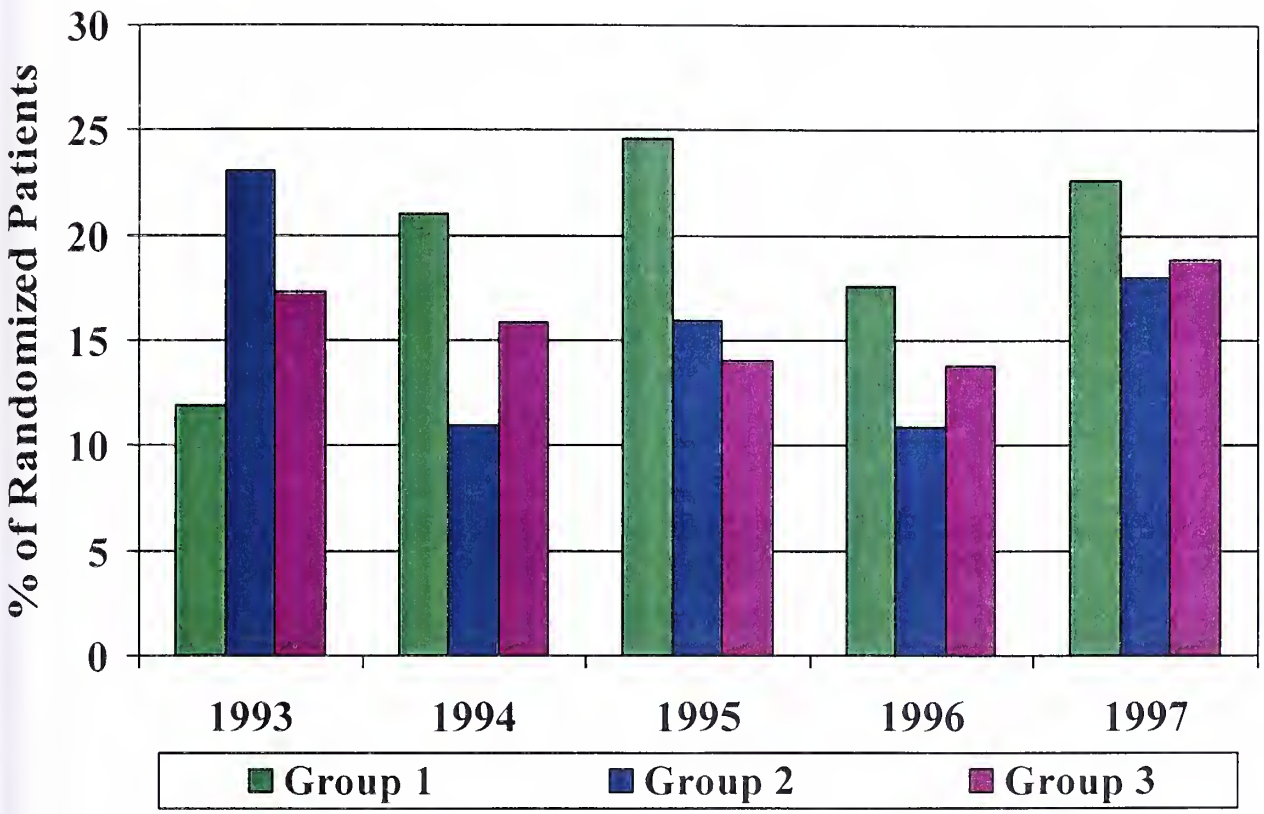

Figure 30. Diuretic Use by Hospital Type by Year. This graphs depicts the percent of CHAMP study patients treated with diuretics according to the hospital type to which they were admitted and depicted over time.

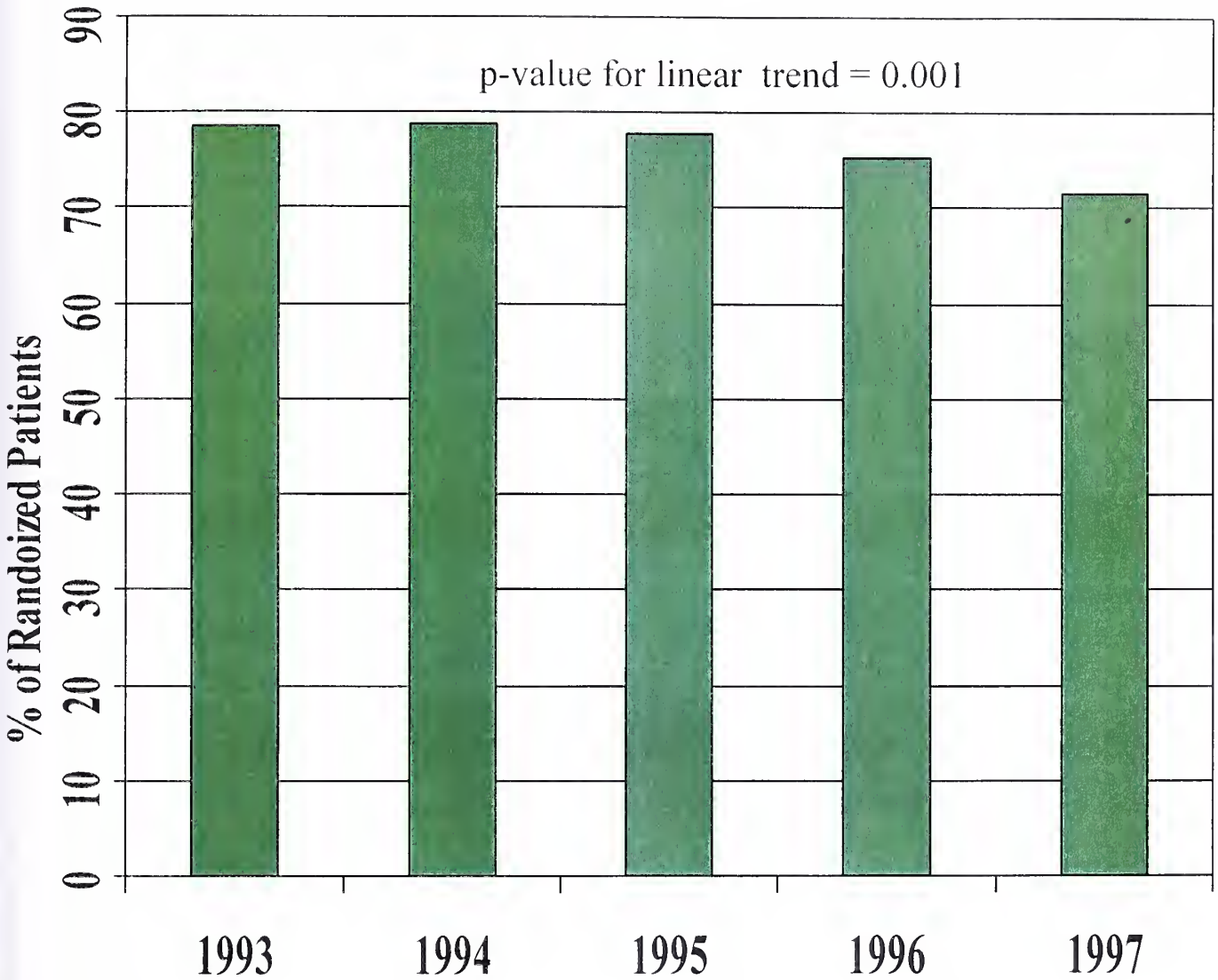

Figure 31. Nitrate Use by Year. This graph depicts the percent of CHAMP study patients treated with nitrates for each year under investigation.

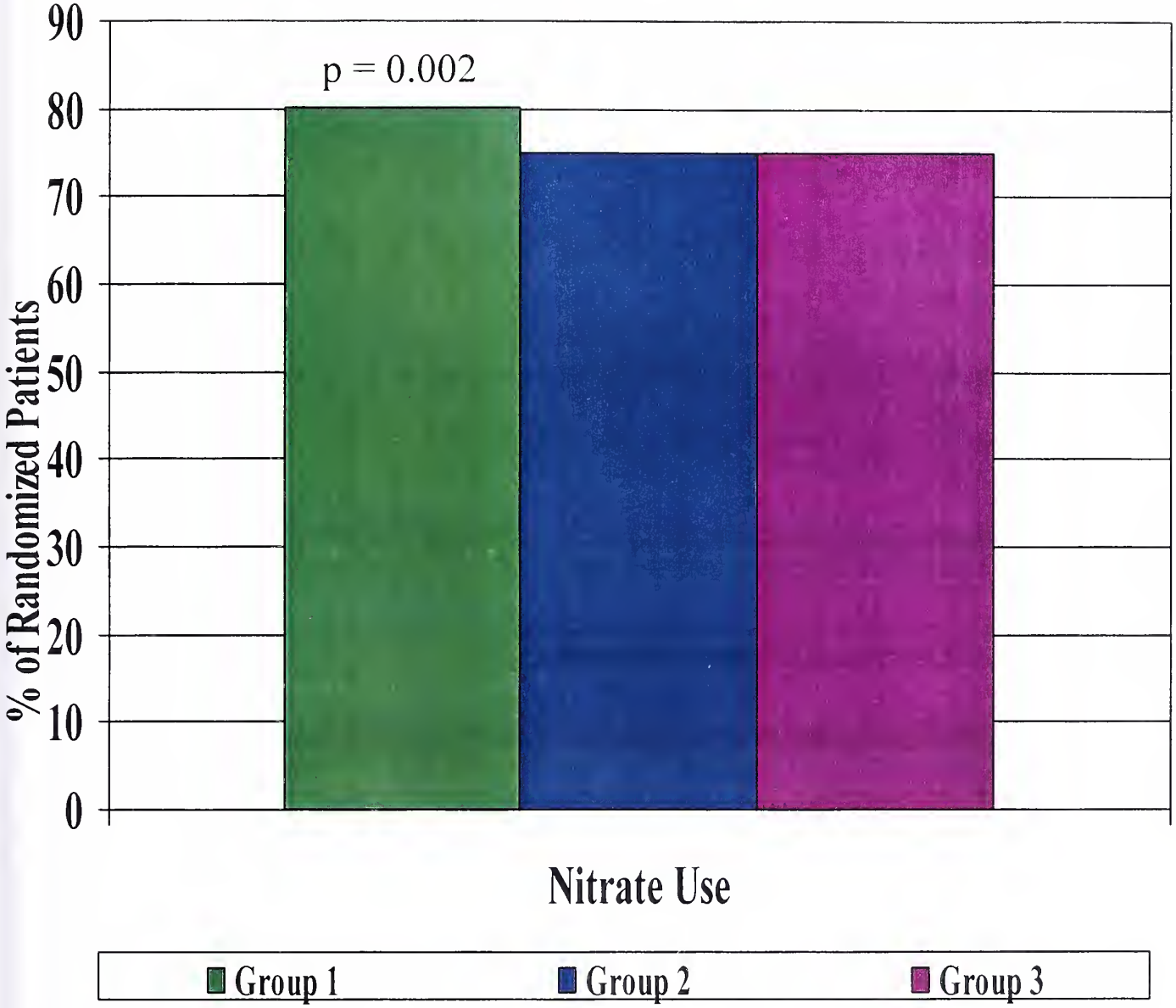

Figure 32. Nitrate Use by Hospital Type. This graph depicts the percent of CHAMP study patients treated with nitrates divided according to the hospital type to which they were admitted.

p-value for linear trend

Group 1	p = 0.005
Group 2	p = 0.109
Group 3	p = 0.001

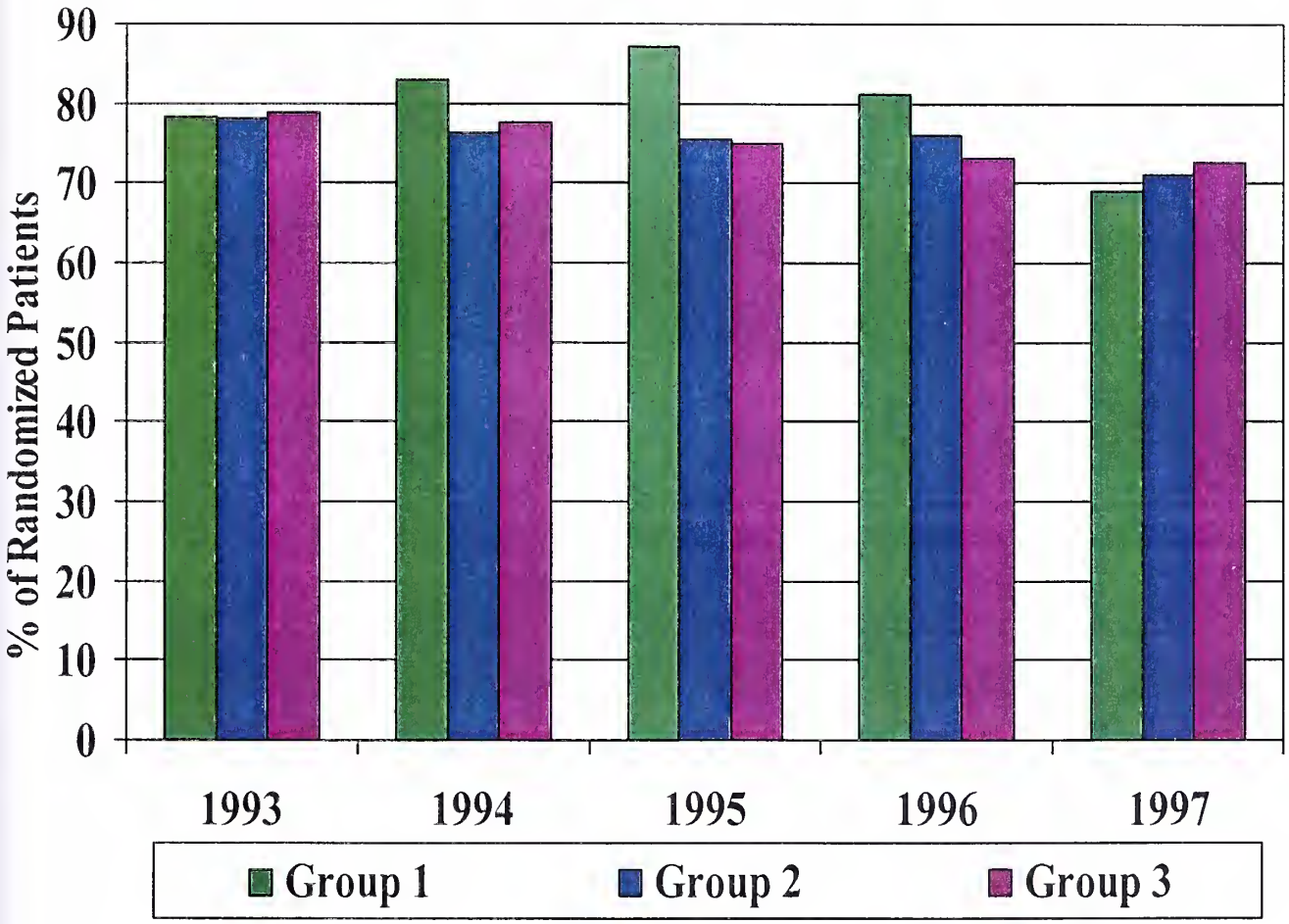

Figure 33. Nitrate Use by Hospital Type by Year. This graphs depicts the percent of CHAMP study patients treated with nitrates according to the hospital type to which they were admitted and depicted over time.

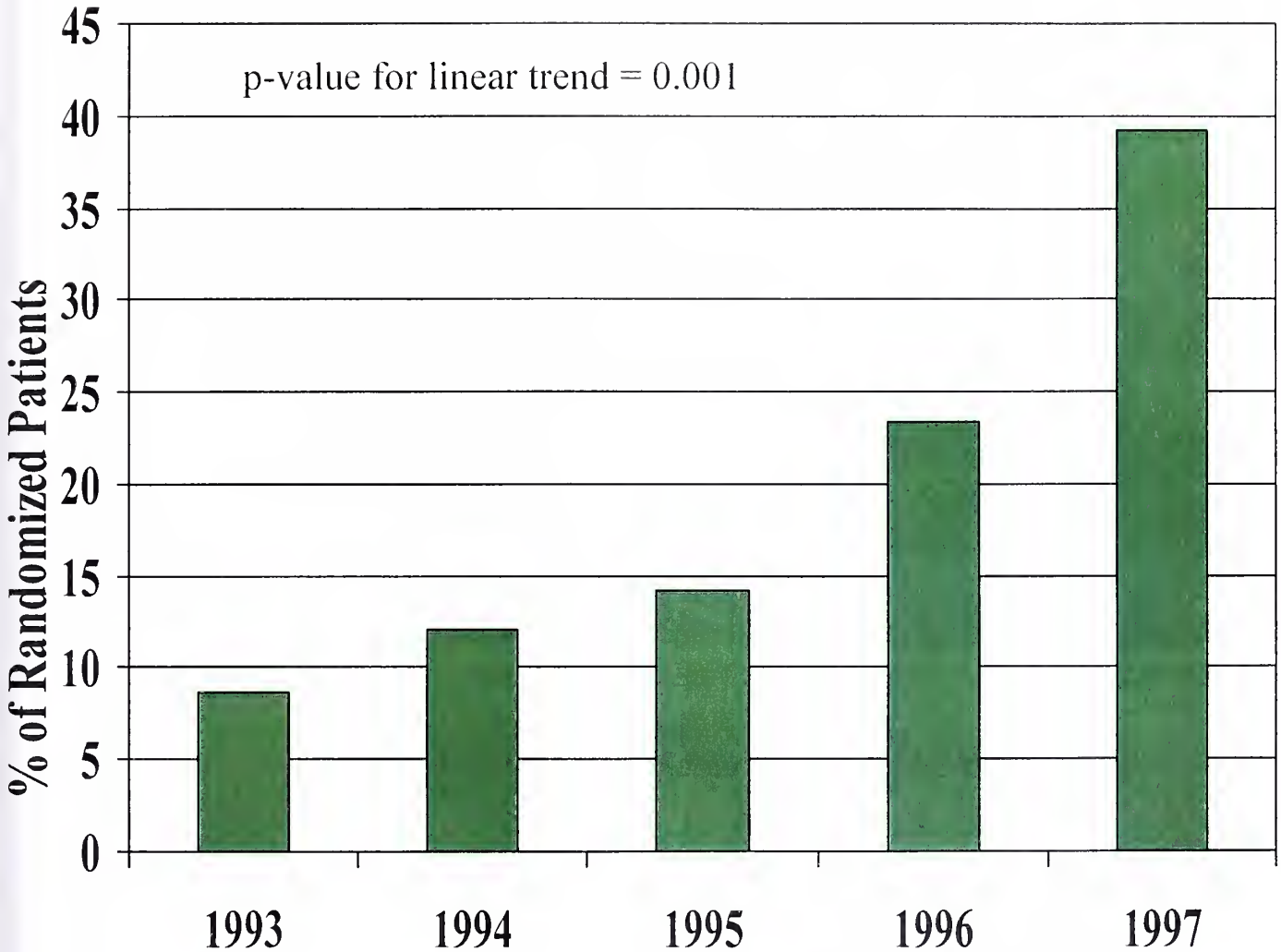

Figure 34. Hypolipidemic Agent Use by Year. This graph depicts the percent of CHAMP study patients treated with hypolipidemic agents for each year under investigation.

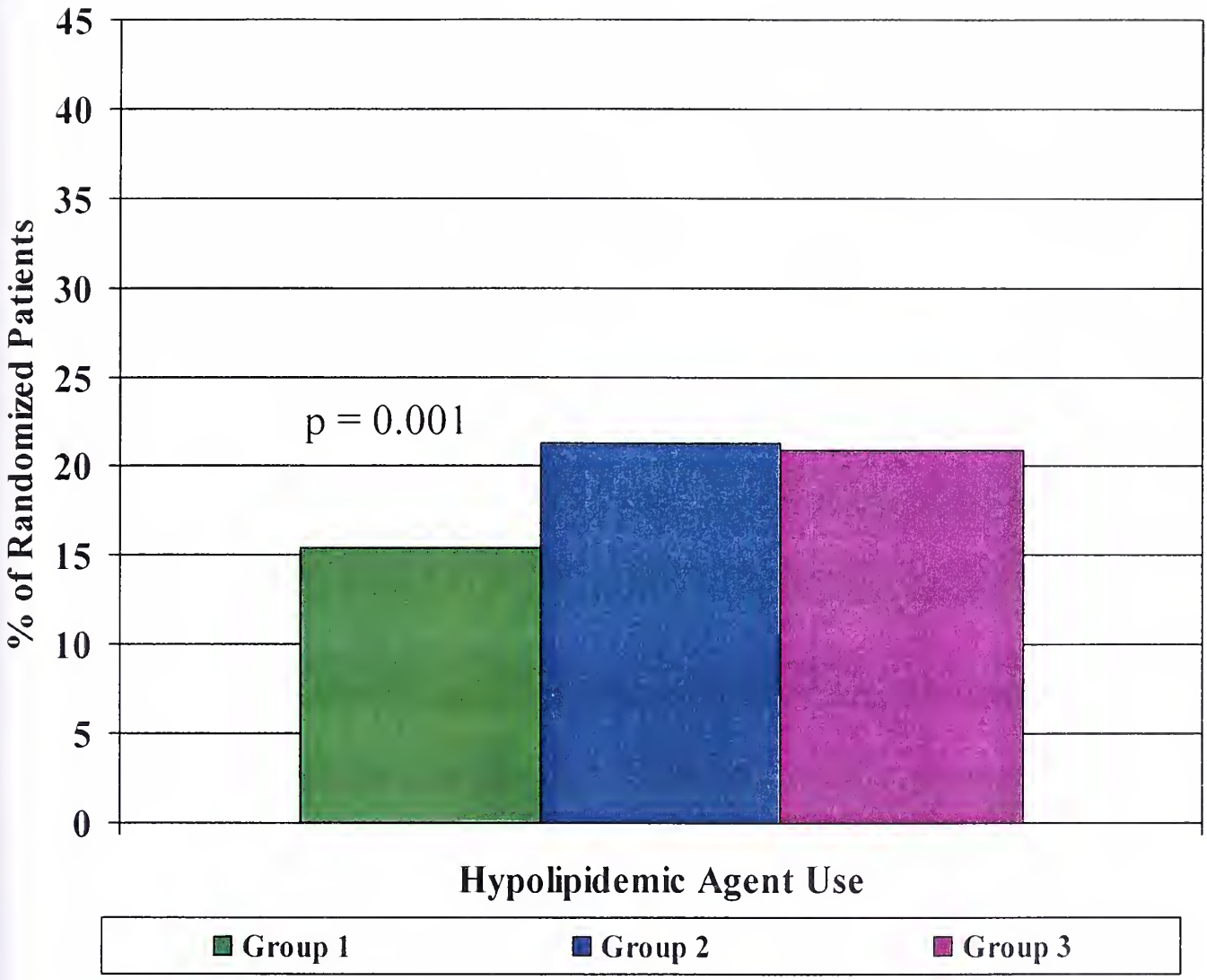

Figure 35. Hypolipidemic Agent Use by Hospital Type. This graph represents the percent of CHAMP study patients treated with hypolipidemic agents divided according to the hospital type to which they were admitted.

p-value for linear trend

Group 1	p = 0.001
Group 2	p = 0.001
Group 3	p = 0.001

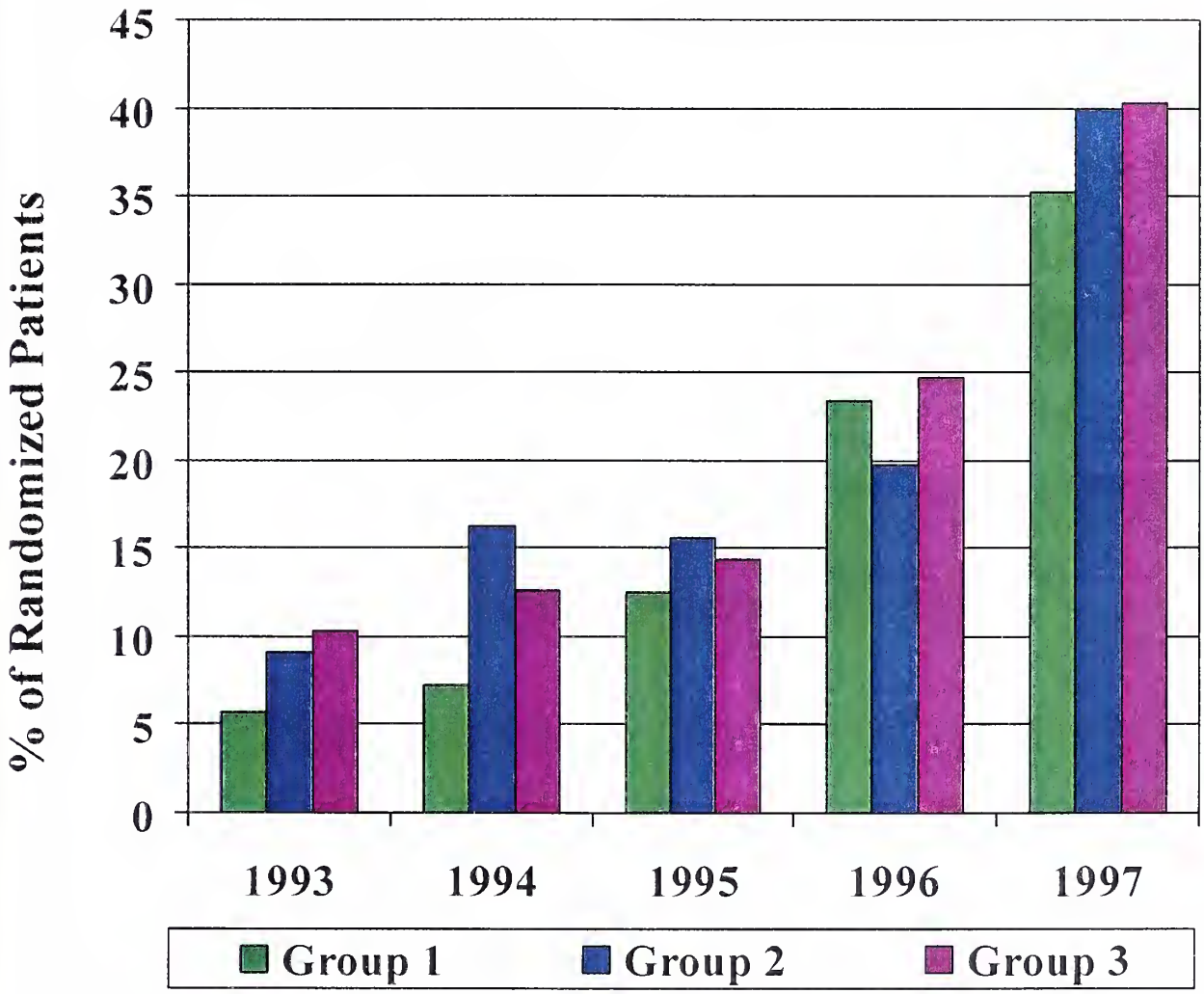

Figure 36. Hypolipidemic Agent Use by Hospital Type by Year. This graphs depicts the percent of CHAMP study patients treated with hypolipidemic agents according to the hospital type to which they were admitted and depicted over time.

VIII. TABLES

Table A. CHAMP Exclusion Criteria

Life expectancy of less than 2 years due to the presence of advanced organ disease or malignancy
The presence of ongoing bleeding or a known predisposition to bleeding such as an acquired or inherited coagulopathy, thrombocytopenia (platelet count < 100,000/mm3), active peptic ulcer disease, a history of clinically significant gastrointestinal bleeding, severe liver disease associated with coagulopathy, dialysis dependent end stage renal disease, or the presence of grade 3 or 4 retinal hemorrhages
The presence of an alternative indication for anticoagulant therapy including any of the following: a cerebral vascular accident complicating the index AMI, the presence of a left ventricular clot, an acute venous thrombosis or pulmonary embolism, the presence of atrial fibrillation or cardiac valve replacement
The presence of a condition requiring treatment with nonsteroidal antiinflammatory drugs or with ASA in doses exceeding 80 mg/d (i.e. rheumatoid arthritis)
Severe uncontrolled hypertension with systolic blood pressure in excess of 180 mm Hg or diastolic blood pressure in excess of 110 mm Hg at time of consideration for randomization. Patients excluded with this condition were able to be rescreened once the blood pressure had been controlled
Personal considerations making follow-up difficult or impractical such as living too far from the center, the presence of severe mental disturbances, or substance abuse
Known hypersensitivity to aspirin or history of significant hemorrhage attributed to aspirin or warfarin therapy in the past

Table B. Information Collected From CHAMP Database

CHAMP Enrollment	Rates of procedure utilization: Early (within 14 days post-MI) CABG Later (between 14-90 days post-MI) CABG Early (within 14 days post-MI) PTCA Later (between 14-90 days post-MI) PTCA	Rates of medication usage: Thrombolytics Ace inhibitors Beta-blockers Calcium channel blockers Digitalis Diuretics Nitrates Hypolipidemic Agents

Table C. Classification System of Hospital Sophistication

Type 1	No cardiac catheterization No cardiac surgery
Type 2	Yes cardiac catheterization No cardiac surgery
Type 3	Yes cardiac catheterization Yes cardiac surgery

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